Exhibit 5

FDA Briefing Document

Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

June 11-12, 2019

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the clinical utility and safety concerns associated with the higher range of opioid analgesic dosing (both in terms of higher strength products and higher daily doses) in the outpatient setting, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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OFFICE DIRECTOR MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of Surveillance and Epidemiology (OSE)

Date:	May 22, 2019
From:	Judy Staffa, Ph.D., R.Ph. Associate Director for Public Health Initiatives Office of Surveillance and Epidemiology, CDER, FDA
To:	Chair, Members and Invited Guests Drug Safety and Risk Management Advisory Committee (DSaRM) Anesthetic and Analgesia Drug Products Advisory Committee (AADPAC)
Subject:	Overview of the June 11-12, 2019 DSaRM/AADPAC meeting

I. Background

FDA is seeking public input on the clinical utility of and safety concerns associated with the higher range of opioid analgesic dosing (both in terms of higher dosage strength products and higher daily doses) in the outpatient setting. FDA is interested in better understanding current clinical use and situations that may warrant use of higher doses of opioid analgesics. We are also interested in discussing the magnitude and frequency of harms associated with higher doses of opioid analgesics relative to lower doses, as well as optimal strategies for managing these risks while ensuring access to appropriate pain management for patients.

FDA frequently hears from patients and healthcare providers, for example, during the 2018 FDA Patient-Focused Drug Development meeting on chronic pain, that higher-dose opioid analgesics continue to be a unique and necessary part of effective pain management for some patients. FDA is also aware of increasing public concern about the risks these products pose to both patients and others in the community; indeed, some stakeholders have asked the Agency to withdraw the approval of higher dosage strength oral and transmucosal opioid analgesics due to safety concerns. Higher dosage strength products may be more harmful in cases of accidental exposure and overdose and may also be more sought out for misuse and abuse. Along with other important factors, a higher daily opioid analgesic dose is associated with greater risk of overdose. Concerns have also been raised that higher dose opioid analgesic regimens may carry a higher risk of addiction, although robust evidence for a causal relationship is lacking. There is a strong association between higher opioid analgesic dose and duration/persistence of opioid analgesic therapy, and the assessment of temporal relationships and independent effects of opioid analgesic

dose and duration on the risks of both addiction and overdose is challenging. In addition, FDA acknowledges the complex and evolving landscape of the opioid epidemic, with myriad federal, state, local, and payer efforts to encourage more judicious prescribing of opioid analgesics, and the growing threat of highly lethal illicit opioids.

To better understand both the clinical utility and harms of higher dose opioid analgesics in the current environment, and to discuss the advantages and disadvantages of potential risk-management strategies designed to limit or target the use of these products, FDA brings these issues to our advisory committees to seek input and advice from the clinical, patient, public health, and research communities.

II. Issues for consideration

Taking any regulatory action requires careful consideration of the potential impacts of that action and the tradeoffs between the desired positive impact and the potential negative impact on patients and on public health. When considering regulatory strategies relating to opioid analgesics, FDA always considers two fundamental public health goals:

1. We want to reduce opioid misuse, abuse, addiction, overdoses and deaths.
2. We want to ensure that products are available to meet the medical needs of people living with debilitating pain.

We also need to ensure that our actions are supported by the best available evidence. Another important goal, therefore, is to strengthen our scientific understanding of the biological and behavioral drivers of misuse, abuse, and addiction, and the risk factors that increase the likelihood of overdose and death.

FDA is increasingly moving toward a systems-based approach to assessing potential regulatory actions that may make meaningful gains in addressing the opioid crisis. This means considering the decisions and behaviors of multiple stakeholders: healthcare providers, patients, communities, insurers and others. It also means fully evaluating the interrelated set of factors that can affect opioid analgesic use, and impact opioid misuse, abuse, addiction, overdose and death. When we consider the potential impact of possible regulatory actions for higher daily doses and higher dosage strength opioid analgesic products considering these actions in the context of the broader system with all of its interrelationships, a number of key uncertainties emerge:

- **What is the extent and nature of the clinical need for higher daily doses of opioid analgesics and, related, the utility of having higher dosage strength products available?** *In this background document, the Division of Anesthesia, Analgesia and Addiction Products (DAAAP's) memo includes information about approved opioid analgesic products, updates on CDC guidelines and concerns about how they have been applied, and highlights from the recently released "Draft Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies and Recommendations," from the Best Practices on Pain Management Task Force. The Division of Epidemiology (DEPI) review describes the prescription patterns and trends for higher dosage strength and higher daily dose opioid analgesics, and also provides data characterizing their clinical use. In addition, we have invited clinicians and patients to present their perspectives on the current need for and use of these products.*

- **What do we know about the relationship between opioid analgesic daily dose, and high dosage strength products, and the risks of abuse, addiction, and overdose? How do other factors, such as duration of use and comorbidities, affect these risks?** *DEPI's review in this background document includes a summary and critical appraisal of the epidemiologic literature in these areas, and several guest speakers will discuss aspects of abuse and addiction to inform discussions about the role of higher daily dose and higher dosage strength products in the risk of abuse, addiction, and overdose. A patient who developed opioid use disorder following treatment with opioid analgesics will also share his experience.*

- **How would any regulatory action to limit or target the use of higher dosage strength opioid analgesic products influence the treatment decisions of healthcare providers and others in the healthcare system? For example, would healthcare providers compensate by prescribing a greater number of lower strength products to achieve a certain daily dose? Would they reduce their patients' daily opioid doses, or even discontinue treating patients who require higher daily doses?** *The DEPI review includes a summary of responses FDA received to a scientific inquiry sent to several health systems about their use and experiences with reducing or restricting use of higher dosage strength opioid analgesic products. We have also invited guest speakers from the Veterans Health Administration and Kaiser Washington to share their experiences, both positive and negative, when programs were implemented to reduce prescribing of higher dose opioid analgesics.*

- **How might any such regulatory action impact patient access to treatment and potentially result in unintended harms to patients, for example uncontrolled pain, psychological distress or suicidality, or seeking other sources of opioids, either prescription or illicit?** *We have invited a guest speaker to discuss opioid analgesic "de-prescribing" and the effects on patients, both positive and negative.*

- **What can we anticipate the effects of any such regulatory action would be on the volume of prescription opioid analgesics available and accessible in the community, resulting from changes in prescribing practices, patient use, and opportunities for diversion?** *The current volume and trends in opioid analgesic prescribing, by dosage strength, of high dosage strength opioid analgesic products, as well as characteristics of patients prescribed these products, is described in the DEPI review. We have also invited guest speakers to discuss the potential for use and abuse of these products by individuals other than those to whom they were prescribed.*

Varying perspectives about these uncertainties can lead to different opinions about what may be the best course of action. Therefore, there is a strong need to bring together the community of stakeholders to consider the collective scientific understanding of the issues relating to higher daily doses and higher dosage strength opioid analgesic products and potential strategies to reduce risks to patient and public health. *A description of various types of FDA regulatory actions to manage risks associated with opioid analgesics, with some examples of actions that have been taken to date, are included in DAAAP's memo.*

III. Questions for discussion

(1) Discuss the role of higher daily doses and high dosage strength products of opioid analgesics in the management of pain.

a. Discuss the settings or patient populations where there may be a clinical need for higher daily doses of opioid analgesics
b. Discuss the specific clinical utility of higher dosage strength opioid analgesic products, relative to lower dosage strength products

(2) Discuss the risks attributable to higher daily doses and higher dosage strength opioid analgesic products relative to lower daily doses and lower dosage strength products. In particular, discuss the differences in risks of misuse and abuse, addiction, and non-fatal or fatal overdose with high relative to lower daily doses or dose strengths

Include in your discussion the influence of therapy duration, physical opioid dependence, and other factors, as well as risks in different patient populations and to others who may access these drugs (e.g., young children, adolescents).

(3) Discuss the potential impact on patient health and public health more broadly if FDA were to take any regulatory actions that resulted in reduced prescribing, access to, and use of higher dosage strength opioid analgesic products, specifically. Consider both positive and negative impacts on patients, healthcare delivery, and public health.

a. What currently available evidence is most compelling in predicting the impacts of taking such actions?
b. What are the most significant uncertainties (e.g., changes in prescribing behavior, rates of transition of patients to illicit drug use) in understanding the ultimate impact of such interventions on patients and public health?
c. What additional evidence could help address these uncertainties?

(4) Considering the discussion on all the previous questions, discuss whether there would be value in FDA taking any new regulatory actions intended to target or reduce prescribing and use of higher dosage strength opioid analgesic products.

a. If FDA were to consider potential new regulatory actions, how might FDA define the products that would be subject to such actions?
b. Discuss any other actions FDA should consider to improve the safety of higher dosage strength opioid analgesic products (i.e., actions not specifically intended to target or reduce prescribing and use).

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

MEMORANDUM

DATE: May 13, 2019

FROM: Ning Hu, MD MS
Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Office of Drug Evaluation II
Office of New Drugs

THROUGH Pamela Horn, MD
Medical Team Leader
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THROUGH Sharon Hertz, MD
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TO: Chair, Members and Invited Guests
Drug Safety and Risk Management Advisory Committee (DSaRM)
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

RE: Opioids Regulatory Background for the June 11-12, 2018, DSaRM/AADPAC Meeting

Background

Opioid analgesic products present unique challenges in clinical practice and public health in that they provide clinically significant analgesic benefit, including for pain for which other analgesics are inadequate, while also carrying serious risks including sedation and respiratory depression. Overdose of an opioid analgesic can result in death. The misuse and abuse of prescription opioids and the associated risks of addiction, overdose, and death are currently a major public

health crisis in the United States.

Unlike other approved analgesic products, most opioid analgesics have no maximum dose because there is no ceiling effect for analgesia. Further, along the range of doses that have been used clinically, no particular dose of any opioid has been determined to be a cutoff point between safe-for-use or unsafe-for-use. The higher the dose, the greater the analgesic effect. However, it is also true that the higher the dose, the greater the risk for serious adverse events.

Physiologic responses to exposure to opioid analgesics include the development of tolerance and physical dependence. These two physiologic processes can complicate the management of patients on opioid analgesics when not recognized and taken into consideration when evaluating each patient. In the setting of chronic pain, over time some patients may require increases in their dose to maintain efficacy, resulting in relatively high doses of opioids. This may be due to the development of tolerance but may also be due to worsening in the underlying pain, or in some cases, the development of opioid-induced hyperalgesia.

Because of the societal harms associated with the over reliance on the use of prescription opioid analgesics, many aspects of the use of opioid analgesics have come under intense scrutiny.

It is important to consider the potential repercussions of well-meaning attempts to address the opioid crisis without adequate scientific evidence to support such actions. Inadequately treated chronic pain has consequences, and in general, the use of higher doses of opioid analgesics often occurs in the setting of chronic pain, as patients titrate to an effective dose. Robust evidence supports that chronic pain itself, regardless of type, is an important independent risk factor for suicidality, as chronic pain patients are at least twice as likely to report suicidal behaviors or to complete suicide.[1] In a national sample of Veterans Health Administration, among patients discontinued from long-term opioid therapy for chronic pain, nearly 12% had documented suicidal ideation and suicidal self-directed violence in the year following discontinuation.[2]

Further, it has been pointed out that rapid forced opioid tapering can destabilize patients with chronic pain, precipitating severe opioid withdrawal accompanied by worsening pain and profound loss of function. To escape the resultant suffering, some patients may seek relief from illicit (and inherently more dangerous) sources of opioids, whereas others may become acutely suicidal.[3]

In support of the idea that there should be absolute limits on the total daily dose of opioid analgesics, many have inappropriately turned to the CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016.[4] The idea behind this guideline was that "improving the

[1] Racine, M. Chronic pain and suicide risk: A comprehensive review. Progress in Neuropsychopharm and Biological Psychiatry 2018; 87:269-280

[2] Demidenko MI, et. al., Suicidal ideation and suicidal self-directed violence following clinician-initiated prescription opioid discontinuation among long-term opioid users, General Hospital Psychiatry 47 (2017) 29–35

[3] International Stakeholder Community of Pain Experts and Leaders Call for an Urgent Action on Forced Opioid Tapering. Pain Medicine. 2019;20: 429-433

[4] https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmmwr%2Fvolumes%2F65%2Frr%2Frr6501e1er.htm

way opioids are prescribed through clinical practice guidelines can ensure patients have access to safer, more effective chronic pain treatment while reducing the number of people who misuse or overdose from these drugs."[5] However, the guidelines were misinterpreted and misapplied, contributing to substantial harms to patients, particularly patients with chronic pain who were forced to taper their previously stable opioid doses to lower doses, or who were forced to discontinue their opioids through forced tapers or patient abandonment. This was captured in a recent statement by the CDC, "CDC Advises Against Misapplication of the *Guideline for Prescribing Opioids for Chronic Pain*".[6] Based on the extent of misapplication that has taken place, and resultant harms, it is worthwhile to note the following key points taken verbatim from this statement:

CDC is raising awareness about the following issues that could put patients at risk:

- **Misapplication of recommendations to populations outside of the Guideline's scope.** The Guideline is intended for primary care clinicians treating chronic pain for patients 18 and older. Examples of misapplication include applying the Guideline to patients in active cancer treatment, patients experiencing acute sickle cell crises, or patients experiencing post-surgical pain.
- **Misapplication of the Guideline's dosage recommendation that results in hard limits or "cutting off" opioids.** The Guideline states, "*When opioids are started*, clinicians should prescribe the lowest effective dosage. Clinicians should… avoid *increasing* dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day." The recommendation statement does not suggest discontinuation of opioids already prescribed at higher dosages.
- **The Guideline does not support abrupt tapering or sudden discontinuation of opioids**. These practices can result in severe opioid withdrawal symptoms including pain and psychological distress, and some patients might seek other sources of opioids. In addition, policies that mandate hard limits conflict with the Guideline's emphasis on individualized assessment of the benefits and risks of opioids given the specific circumstances and unique needs of each patient.
- **Misapplication of the Guideline's dosage recommendation to patients receiving or starting medication-assisted treatment for opioid use disorder.** The Guideline's recommendation about dosage applies to use of opioids in the management of chronic pain, not to the use of medication-assisted treatment for opioid use disorder. The Guideline strongly recommends offering medication-assisted treatment for patients with opioid use disorder.

On May 9 and 10, 2019, the Best Practices in Pain Management Task Force met to finalize consensus on the "Draft Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations."[7] The Comprehensive Addiction and Recovery Act (CARA) of 2016 led to the creation of the Pain Management Best Practices Inter-Agency Task

[5] https://www.cdc.gov/drugoverdose/prescribing/guideline.html
[6] https://www.cdc.gov/media/releases/2019/s0424-advises-misapplication-guideline-prescribing-opioids.html
[7] https://www.hhs.gov/ash/advisory-committees/pain/meetings/2019-05-09/index.html

Force whose mission has been to determine whether gaps in or inconsistencies between best practices for acute and chronic pain management exist and to propose updates and recommendations to those best practices. The recommendations of the Task Force will be finalized and submitted to Congress in 2019.

Some of the strengths of this report include the use of 29 clinical and academic experts with decades of experience in the fields of pain management, patient advocacy, substance use disorders, and mental health; and the open, public nature of the report, its deliberations, and opportunity to receive and receive patient testimonials and public meeting comments, including approximately 6,000 comments from the public submitted during a 90-day public comment and 3,000 comments from 2 public meetings. Relevant to the topic at hand, the task force did not recommend any absolute limits on the individual dose or total daily dose of opioid analgesics. Rather, the task force concluded that emphasis should be placed on the importance of individualized care, the use of multimodal approaches to acute pain management, and the use of multidisciplinary approaches to chronic pain management. The executive summary of this report has been appended to this memo.

This meeting presents an opportunity to examine whether the role of higher dose opioids for chronic painful conditions in the outpatient setting is warranted.

The following are definitions of important terms related to opioid analgesics.

- Analgesic tolerance is the need for increasing doses of opioids to maintain a defined analgesic effect[8] (in the absence of disease progression or other external factors). It exhibits a wide individual variability during opioid therapy.

- Physical dependence results in a physical disturbance (withdrawal symptoms) after abrupt discontinuation or a significant dosage reduction of a drug[9].

  Tolerance and physical dependence are physiological changes that develop during chronic opioid therapy. Abuse and addiction are separate and distinct from physical dependence and tolerance.

- Addiction[10] is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

  Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or

[8] Opioid analgesic products labeling, such as OxyContin (NDA 22272), Hysingla ER (206627), etc. Section 9, "DRUG ABUSE AND DEPENDENCE"
[9] Ibid.
[10] American Society of Addiction Medicine. Public Policy Statement: Definition of Addiction. Short Definition of Addiction.

engagement in recovery activities, addiction is progressive and can result in disability or premature death.

- Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.[11]

These phenomena are separate and distinct. Having developed tolerance and physical dependence to opioids is not the same as having an addiction to opioids and can develop in the absence of abuse or addiction. Conversely, addiction may not always be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

Chronic pain is defined as ongoing or recurrent pain that lasts beyond the usual course of acute illness or injury healing and adversely affects an individual's well-being. Pain is typically considered chronic when it lasts more than three months in duration.

Opioid Analgesic Products for Outpatient Use

FDA has approved a variety of extended-release/long-acting (ER/LA) and immediate-release (IR) opioid analgesics and combination opioid/non-opioid products for outpatient use. The product labeling contains a summary of the essential scientific information needed for the safe and effective use of the drug. The following information is included in opioid product labeling:

- Indications

  The primary role of the INDICATIONS AND USAGE section of labeling for opioid analgesics is to enable health care practitioners to readily identify appropriate therapies for the context of use. In opioid analgesic labeling, ER/LA opioid products are indicated for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, and the IR opioid products are indicated for management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The indications are worded this way to alert the prescriber that opioids should be used when alternatives have not or are not expected to be adequate for the pain that the patient is experiencing to better balance the benefit-risk profile of the opioid analgesic.

- Conversion information and equianalgesic doses

  The purpose of opioid conversion information in the product labeling is to enable pain management practitioners to safely convert a patient from an existing opioid regimen to another and not to facilitate equianalgesic conversion.

[11] Opioid analgesic products labeling, such as OxyContin (NDA 22272), Hysingla ER (206627), etc. Section 9, "DRUG ABUSE AND DEPENDENCE"

Conversion information and conversion factors are included in the DOSAGE AND ADMINISTRATION section in opioid products' labeling. The conversion information is based on the clinical trial data for the specific product and attempts to account for incomplete cross-tolerance among different opioid products. For this reason, the information should only be used to convert to the specific opioid for which the label was written from the other opioid products listed.

The conversion information/factors in product labeling neither describes equianalgesic conversion (the dose at which two analgesics (at steady state) provide approximately the same pain relief[12]) nor suggests that the doses will have the same adverse reactions or euphoric effects. Equianalgesic ratios are difficult to establish because multiple factors can influence the accurate estimation of analgesia, such as incomplete cross-tolerance among different opioid products, wide individual variability in opioid tolerance due to genetic factors, and previous opioid use.

- Tolerance criteria and requirements

Because of the wide variability of individual tolerance, the opioid product labeling recommends a conservative approach when determining the initial and total daily dosage of the drug based on the patient's level of tolerance. High dosage strengths and high total daily dose (TDD) are only for use in opioid-tolerant patients. Based on clinical trial data, a practical definition for opioid tolerant has been developed. In this context, patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

Some opioid products are only indicated for use in opioid-tolerant patients. With the consideration of individual variability, the clinician may individually titrate the drug to a dose that provides adequate analgesia and minimizes adverse reactions based on the patient's response.

Extended release/long-acting (ER/LA) opioid analgesic products

A summary of extended release/long-acting (ER/LA) opioid products is shown in Table 1. ER/LA opioid products are approved with the indication of management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Nucynta ER (Tapentadol, NDA 200533) is further indicated for the treatment for neuropathic pain associated with diabetic peripheral neuropathy (DPN). ER/LA opioids are not limited to a maximum daily dose based on their activity at the opioid receptor because opioids have neither a ceiling effect nor uniform therapeutic plasma levels. The general approach is to initiate opioid treatment with a low dose and individually titrate to a tolerable dose that provides adequate analgesia. The products that have a maximum daily dose (MDD) defined

[12] Shaheen, Philip E et al. "Opioid Equianalgesic Tables: Are They All Equally Dangerous?" Journal of pain and symptom management. 38.3 409–417. Web.

are Nucynta ER (Tapentadol, NDA 200533) and Conzip (Tramadol, NDA 22370) given their possible combined mechanism of action of mu-opioid receptor (MOR) agonist and serotonin/norepinephrine reuptake inhibitor (SSRI/NRI) and the dose-response relationship for toxicity with respect to the SSRI/NRI activity and Butrans (buprenorphine, NDA 21306 and Belbuca (buprenorphine, NDA 207932) based on the potential for QTc interval prolongation. Duragesic (Fentanyl Citrate, NDA 19813) and Exalgo (Hydromorphone Hydrochloride, NDA 21217) are only indicated for use in opioid-tolerant patients.

Table 1. Extended-release/long-acting (ER/LA) opioid products

Product name NDA# Date of approval	API	Dosage forms Formulation/route Strengths	Dosing regimen Dosage and administration based on opioid tolerance[a]
Butrans 21306 06/30/2010	Buprenorphine	• Transdermal system • 5 mcg, 7.5 mcg, 10 mcg, 15 mcg, 20 mcg/hour	• 7.5, 10, 15, and 20 mcg/hour are only for use in opioid-experienced[b] and tolerant patients • Opioid-naïve patients: initiate with a 5 mcg/hour patch. • MDD 20 mcg/hour based on potential for QT interval prolongation
Belbuca 207932 10/23/2015	Buprenorphine Hydrochloride	• Buccal film • 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg	• For opioid-naïve patients: 75 mcg once daily or q12h • 600 mcg, 750 mcg, and 900 mcg are only for use following titration • MDD 900 mcg q12h based on potential for QT interval prolongation
Duragesic 19813 08/07/1990	Fentanyl Citrate	• Transdermal system • 12 mcg, 25 mcg, 37.5 mcg, 50 mcg, 75 mcg and 100 mcg/hour	• For opioid-tolerant patients only • Each transdermal system is intended to be worn for 72 hours
Zohydro ER 202880 10/25/2013	Hydrocodone Bitartrate	• Oral capsules • 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg	• A single dose > 40 mg, or TDD > 80 mg are only for use in opioid tolerant patients • For opioid-naïve and opioid non-tolerant patients: start 10 mg q12h
Hysingla ER[c] 206627 11/20/2014	Hydrocodone Bitartrate	• Oral tablets • 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg	• TDD > 80 mg are only for use in opioid tolerant patients • For opioid-naïve patients: initiate with 20 mg q24h
Exalgo[d] 21217 03/01/2010	Hydromorphone Hydrochloride	• Oral tablets • 8 mg, 12 mg, 16 mg, 32 mg	• For opioid-tolerant patients only q24h
Opana ER[e] 21610 06/22/2006	Oxymorphone Hydrochloride	• Oral tablets • 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg	• Opioid-naïve and non-tolerant patients, initiate with 5 mg q12h
Dolophine 6134 08/13/1947	Methadone hydrochloride	• Oral tablets • 5 mg and 10 mg	• Opioid-naïve patients: initiate 2.5 mg every 8 to 12 hours and titrate up no more frequent than every 3 to 5 days
Arymo ER[c] 208603 01/09/2017	Morphine Sulfate	• Oral tablets • 15 mg, 30, mg, 60 mg	• > 60 mg, or a TDD > 120 mg are only for use in opioid-tolerant patients: • For opioid-naïve and opioid non-tolerant patients: start 15 mg q 8 or 12 h
Kadian 20616 07/03/1996	Morphine Sulfate	• Oral capsules • 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200 mg	• 100 mg or 200 mg tablets daily, a single dose > 60 mg, or a TDD > 120 mg are only for use in opioid-tolerant patients • For opioid-naïve patients: start with IR morphine, then convert to Kadian • For opioid non-tolerant patients: initiate with a 30 mg daily
MS Contin 19516 05/29/1987	Morphine Sulfate	• Oral tablets • 15 mg, 30 mg, 60 mg, 100 mg, 200 mg	• 100 mg and 200 mg tablets, a single dose > 60 mg, or a TDD > 120 mg only are only for use in opioid tolerant patients • For opioid-naïve and non-tolerant patients: initiate with 15 mg every 8 to 12 hours

Embeda[c] 22321 08/13/2009	Morphine Sulfate and Naltrexone Hydrochloride	• Oral capsules • 20 mg /0.8 mg, 30 mg /1.2 mg, 50 mg /2 mg, 60 mg /2.4 mg, 80 mg /3.2 mg, 100 mg /4 mg	• 100/4 mg, single dose of 60 mg/2.4 mg, TDD > 120 mg/5 mg. q24h are only for use in opioid tolerant patients • For Opioid-naïve and opioid non-tolerant patients, initiate with 20 mg/0.8 mg q24h
MorphaBond ER[c] 206544 10/02/2015	Morphine Sulfate	• Oral tablets • 15 mg, 30 mg, 60 mg, 100 mg	• 100mg tablets, a single dose > 60 mg, or a TDD > 120 mg are only for use in opioid tolerant patients • For opioid-naïve and opioid non-tolerant patients: start 15 mg q8h or q12h
OxyContin[cf] 22272 04/05/2010	Oxycodone Hydrochloride	• Oral tablets • 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg.	• 60 and 80 mg, a single dose > 40 mg, or a TDD > 80 mg, q12h are only for use in opioid-tolerant patients • For opioid-naïve and non-tolerant adults: start 10 mg q12h
Xtampza ER[c] 208090 04/26/2016	Oxycodone	• Oral Capsules • 10 mg, 15 mg, 20 mg, 30 mg, 40 mg	• A TDD > 80 mg or a single dose > 40 mg are only for use in opioid-tolerant patients • For opioid-naïve and opioid non-tolerant patients: 10 mg q12h
Nucynta ER[gh] 200533 08/25/2011	Tapentadol	• Oral tablets • 50 mg, 100 mg, 150 mg, 200 mg, 250 mg	• Opioid-naïve and non-tolerant patients: start 50 mg q12h • MDD: 500 mg per day
Conzip ER[g] 22370 Tramadol	Tramadol hydrochloride	• Oral capsules • 100 mg, 200 mg and 300 mg	• For opioid-naïve and opioid non-tolerant patients, start with 100 mg once daily • MDD: 300 mg per day

[a] Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.
[b] Patients who are opioid-experienced are those receiving, for one week or longer, daily opioid doses up to 80 mg/day of oral morphine or an equianalgesic dose of another opioid.
[c] Abuse-deterrent properties are described in labeling
[d] Discontinued and generics available.
[e] Discontinued and generics available; Opana ER NDA 201655 withdrawn for formulation-specific safety reasons.
[f] The Indication also includes opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.
[g] Products that have a MDD defined.
[h] The product is also indicated for neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Abbreviations: NDA: new drug application; API: active pharmaceutical ingredient; TDD: total daily dose; MDD: maximum daily dose.

Immediate-release (IR) opioid analgesic products

A summary of immediate-release (IR) opioid analgesic products with approved new drug applications (i.e., non-generic opioid analgesic products) is shown in Table 2. IR oral opioid products are approved with the indication of management of pain severe enough to require an opioid agonist and for which alternative treatments are inadequate. Several products are specifically indicated for the management of "acute pain". A group of transmucosal immediate-release fentanyl (TIRF) products are indicated for management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Similar to ER/LA opioid

products, most of the IR opioids have no maximum daily dose defined except tapentadol and tramadol products, fixed dose combination products, and TIRF products as detailed in Table 2.

Numerous generic immediate-release (IR) opioid analgesics and combination opioid/non-opioid products are approved for outpatient use in management of pain severe enough to require an opioid agonist and for which alternative treatments are inadequate. Available IR generic opioid products include products with meperidine, levorphanol, tramadol, tapentadol, codeine, hydrocodone, benzhydrocodone, oxycodone, morphine, oxymorphone, hydromorphone, and fentanyl APIs. They are available in single-entity opioids and in combination with non-opioid analgesic drugs including acetaminophen, aspirin, and ibuprofen, butalbital, and caffeine. Some combination opioid/non-opioid products only have generic products available. Those products have a MDD defined due to dose-dependent toxicity of the non-opioid analgesic APIs.

Table 2. Immediate-release (IR) opioid products

Product name NDA# Date of approval	APIs	Dosage forms Formulation/routes Strengths	Dosing regimen Max daily dosing (MDD)
Products for oral route of administration			
Apadaz[a] 208653 2/23/2018	Benz-hydrocodone /APAP	• Oral tablets • 6.12 mg benzhydrocodone (equivalent to 6.67 mg benzhydrocodone hydrochloride) and 325 mg acetaminophen	• 1 or 2 tablets every 4 to 6 hours as needed for pain • MDD: Not exceed 12 tablets in a 24 hour period
Codeine 22402 7/16/2009	Codeine sulfate	• Oral tablets • 15 mg, 30 mg, and 60 mg	• 15 to 60 mg every 4 hours as needed
Codeine 202245 6/30/2011	Codeine sulfate	• Oral solution • 30 mg/5 mL (6 mg/mL)	• Initiate treatment with 15 to 60 mg (2.5 mL to 10 mL) every 4 hours as needed.
Fioricet w/ Codeine 20232 7/30/1992	Codeine/ APAP/butalbital/caffeine	• Oral capsules • 50 mg butalbital, 325 mg acetaminophen, 40 mg caffeine, and 30 mg codeine phosphate	• Initiate treatment with one or two capsules every 4 hours as needed for pain • MDD: Not exceed 6 capsules
Fioricet w/ Codeine 19429 10/26/1990	Codeine/ aspirin/ butalbital/ caffeine	• Oral capsules • 50 mg butalbital, 325 mg aspirin, 40 mg caffeine, and 30 mg • codeine phosphate	• Initiate treatment with one or two capsules every 4 hours. • MDD: Not exceed 6 capsules
Synalgos-DC 11483 7/7/1958	Dihydrocodeine/ aspirin/caffeine	• Oral capsules • 356.4 mg aspirin, 30 mg caffeine, and 16 mg dihydrocodeine bitartrate	• Initiate treatment with two capsules orally every 4 hours as needed for pain
Dilaudid 19891 12/7/1992	Hydromorphone	• Oral solution: 5 mg/5 mL (1 mg/mL) • Oral tablets: 2 mg, 4 mg, and 8 mg	• Oral solution: one-half (2.5 mL) to two teaspoonfuls (10 mL), 2.5 mg to 10 mg, every 3 to 6 hours • Oral tablets: 2 mg to 4 mg, orally, every 4 to 6 hours.
Dilaudid 19892 12/7/1992	Hydromorphone	• Oral solution: 5 mg/5 mL (1 mg/mL) • Oral tablets: 2 mg, 4 mg, and 8 mg	• Oral solution: one-half (2.5 mL) to two teaspoonfuls (10 mL), 2.5 mg to 10 mg, every 3 to 6 hours • Oral tablets: 2 mg to 4 mg, orally, every 4 to 6 hours.

Levo-Dromoran[b] 8720 12/19/1991	Levorphanol	• Oral tablets • 2 mg	• Initiate treatment in a dosing range of 1 to 2 mg every 6 to 8 hours as needed for pain
Demerol 5010 11/10/1942	Meperidine	• Oral tablets: 50 mg and 100 mg • Oral solution: 50 mg/5mL (10 mg/mL)	• Adult Patients: Start with 50 mg to 150 mg every 3 to 4 hours as needed for pain. • Pediatric Patients: Start with 1.1 mg/kg to 1.8 mg/kg orally, up to the adult dose, every 3 or 4 hours as needed for pain
Morphine 22195 3/17/2008	Morphine	• Oral solution • 10 mg per 5 mL (2 mg/mL), 20 mg per 5 mL (4 mg/mL), 100 mg per 5 mL (20 mg/mL)	• 10 to 20 mg every 4 hours as needed.
Morphine 22207 3/17/2008	Morphine	• Oral tablets • 15 mg and 30 mg	• 15 to 30 mg every 4 hours as needed.
Morphine 201517 6/23/2011	Morphine	• Oral solution • 100 mg/5 mL (20 mg/mL)	• 10 mg to 20 mg (0.5 mL to 1 mL) every 4 hours as needed
Roxybond[c] 209777 04/20/2017	Oxycodone hydrochloride	• Oral tablets • 5 mg, 15 mg, 30 mg	• 5 to 15 mg every 4 to 6 hours as needed for pain.
Roxicodone 21011 8/31/2000	Oxycodone	• Oral tablets • 5 mg, 15 mg, 30 mg	• Initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain.
Oxycodone 200534 10/20/2010	Oxycodone	• Oral capsules • 5 mg	• Initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain
Oxycodone 200535 10/20/2010	Oxycodone	• Oral solution • 5 mg per 5 mL (1 mg/mL), 100 mg per 5 mL (20 mg/mL)	• Initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain.
Oxycodone 201194 1/12/2012	Oxycodone	• Oral solution • 5 mg per 5 mL	• Initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain.
Oxaydo 202080 6/17/2011	Oxycodone	• Oral tablets • 5 mg and 7.5 mg oxycodone HCl	• For opioid naïve patients, initiate treatment with 5 mg to 15 mg every 4 to 6 hours as needed for pain
Percodan 7337 4/12/1950	Oxycodone/ aspirin	• Oral tablets • Oxycodone Hydrochloride 4.8355 mg/ Aspirin 325 mg	• One tablet every 6 hours as needed for pain • MDD: aspirin should not exceed 4 grams or 12 tablets.
Opana[d] 21611 6/22/2006	Oxymorphone	• Oral tablets • 5 mg and 10 mg	• Initiate treatment with 10 to 20 mg orally every four to six hours
Nucynta 22304 11/20/2008	Tapentadol	• Oral tablets • 50 mg, 75 mg, 100 mg	• Initiate at 50 mg, 75 mg, or 100 mg every 4 to 6 hours • Daily doses > 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are not recommended.
Nucynta[d] 203794 10/15/2012	Tapentadol	• Oral solution • 20 mg/mL	• Initiate at 2.5 mL (50 mg), 3.75 mL (75 mg), or 5 mL (100 mg) every 4 to 6 hours • Daily doses greater than 700 mg on the first day of therapy and 600 mg on

			subsequent days have not been studied and are not recommended
Ultram 20281 3/3/1995	Tramadol	• Oral tablets • 50 mg	• Start at 25 mg/day and titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day • MDD: Not to exceed 400 mg/day
Ultracet[d] 21123 8/15/2001	Tramadol/APAP	• Oral tablets • Tramadol hydrochloride 37.5 mg and acetaminophen 325 mg	• Initiate treatment with two tablets every 4 to 6 hours as needed for pain relief • MDD: 8 tablets per day
Transmucosal immediate-release fentanyl (TIRF)[e]			
Subsys 202788 01/04/2012	Fentanyl	• Sublingual spray • 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg dosage strengths.	• Initiate treatment with 100 mcg, individually titrate • Wait at least 4 hours between dosing • Limit consumption to four or fewer doses per day once successful dose is found.
Lazanda 22569 06/30/2011	Fentanyl	• Nasal spray • 100 mcg, 300 mcg or 400 mcg fentanyl base in a 5 mL bottle containing 8 sprays	• Initial dose: 100 mcg (single spray into one nostril), individually titrate • Wait at least 2 hours between dosing • No more than four doses per 24 hours
Abstral 022510 01/07/2011	Fentanyl	• Sublingual tablets • 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg strengths as fentanyl base	• Initial dose: 100 mcg, individually titrate • No more than two doses per breakthrough pain episode • Wait at least 2 hours between dosing • Limit to treat four or fewer breakthrough pain episodes per day once a successful dose is found
Fentora 21947 09/25/2006	Fentanyl	• Buccal tablets • 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base.	• Initial dose: 100 mcg, individually titrate • Wait at least 4 hours between dosing • No more than two doses per breakthrough pain episode
Actiq[f] 20747 11/04/1998	Fentanyl citrate	• Solid oral transmucosal lozenge • 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg	• Initial dose: 200 mcg. Prescribe an initial supply of six 200 mcg ACTIQ units, individually titrate • No more than two doses per breakthrough pain episode • Wait at least 4 hours between dosing • Limit to four or fewer units per day once successful dose is found

[a] Indicated for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
[b] Discontinued; generics available.
[c] Discontinued. Abuse-deterrent properties are described in labeling.
[d] Indicated for management of acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate.
[e] Indicated for management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
[f] Indicated for cancer patients 16 years of age and older
Abbreviations: NDA: new drug application; API: active pharmaceutical ingredient; TDD: total daily dose; MDD: maximum daily dose.

Examples of FDA Regulatory Actions to Manage Risks and Benefits of Opioid Products

When the risks and benefits of a product change or new information becomes available, there are several potential regulatory actions that FDA can take to inform stakeholders and protect the public health. These actions include requiring safety labeling changes based on new safety information, requiring a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the product outweigh the risks, requiring postmarketing studies based on new safety information (including information about reduced effectiveness), and requesting that a Sponsor withdraw their product from the market. Examples of actions that FDA has taken related to opioid products include:

Safety Labeling Changes

On September 27, 2007, the President signed the FDA Amendments Act (FDAAA; Public Law 110-85). Section 901 of Title IX of FDAAA amended the Food Drug & Cosmetic (FD&C) Act by adding new section 505(o). Section 505(o)(4), as codified by FDAAA,[13] authorized FDA to require and, if necessary, order labeling changes if FDA becomes aware of new safety information that FDA believes should be included in the labeling of the drug. Section 505(o)(4) of the FD&C Act imposes time frames for application holders to submit and for FDA staff to review such changes and gives FDA new enforcement tools to bring about timely and appropriate safety labeling changes.

FDA has required multiple safety labeling changes to opioid analgesic products since 2007. Most of these changes were made to the Warnings and Precautions section or by adding or modifying a Boxed Warning. The current Boxed Warnings and Warnings and Precautions sections of the product label convey information about the following risks of opioid analgesics:

BOXED WARNINGS

- Addiction, Abuse, and Misuse
- Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
- Life-Threatening Respiratory Depression
- Accidental Ingestion
- Neonatal Opioid Withdrawal Syndrome
- Cytochrome P450 3A4 Interaction
- Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

WARNINGS AND PRECAUTIONS:

- Addiction, Abuse, and Misuse
- Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
- Life-Threatening Respiratory Depression
- Neonatal Opioid Withdrawal Syndrome

[13] The Substance Use–Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (Publ. L. 115-27), enacted in October 2018, further authorized FDA to require postmarketing studies to assess reduced effectiveness of a drug, or labeling changes based on new effectiveness information.

- Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers
- Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
- Adrenal Insufficiency
- Severe Hypotension
- QTc Interval Prolongation
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
- Risks of Use in Patients with Gastrointestinal Conditions
- Increased Risk of Seizures in Patients with Seizure Disorders
- Withdrawal
- Risks of Driving and Operating Machinery

Risk Evaluation and Mitigation Strategy (REMS)

A REMS is a drug safety program that the FDA can require for certain medications to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication. While all medications have labeling that informs health care stakeholders about medication risks, only a subset of approved medications require a REMS.

Section 505-1 of the FD&C Act authorizes the FDA to require pharmaceutical sponsors to develop and comply with a REMS for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. The elements of a REMS can include a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose, elements to assure safe use, and an implementation system. FDAAA also requires that all REMS approved for drugs or biological products under New Drug Applications (NDA) and Biologics License Applications (BLA) have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

FDA has required REMS for several individual and classes of opioid analgesic products. Below are examples of those programs.

Opioid Analgesic (OA) REMS

The OA REMS is intended to reduce risks and improve safe use of opioid analgesics while continuing to provide access to these medications for patients in pain. The central component of the OA REMS is an education program for healthcare providers (HCPs), including prescribers, nurses, and pharmacists, involved in the treatment and monitoring of patients with pain. Under the OA REMS, application holders are required to make education programs available to HCPs. The application holders are meeting this requirement by providing educational grants to accredited continuing education (CE) providers who offer training to HCPs at no or nominal cost. To be considered compliant with the OA REMS, the CE courses are required to include the content and messages of a "blueprint" developed by FDA for this purpose. The currently approved FDA Blueprint, *FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain*, focuses on the fundamentals of acute and chronic pain management and provides a contextual framework for the safe prescribing of opioid analgesics.

Transmucosal immediate-release fentanyl (TIRF) REMS

The TIRF medicines are approved under a shared system REMS known as the TIRF REMS Access program (TIRF REMS) to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors. The TIRF REMS requires that: 1) outpatient prescribers of TIRF medicines are specially certified; 2) outpatient and inpatient pharmacies that dispense TIRF medicines are specially certified; 3) patients must sign a patient-prescriber agreement form (PPAF) to receive TIRF medicines in an outpatient setting; and 4) distributors may only supply TIRF medicines to certified pharmacies.

Earlier this year, the Agency notified all application holders of TIRF medicines that the TIRF REMS must be modified to ensure that patients are opioid-tolerant *prior* to receiving a TIRF medicine, and to better capture adverse events of interest. This action was based on data in the assessment reports, submitted by the TIRF REMS Industry Group (TRIG), that shows the use of TIRF medicines in opioid non-tolerant patients. The Agency is also requiring the addition of a patient registry for patients that are prescribed a TIRF medicine in an outpatient setting. Currently available data have been insufficient to monitor the adverse events in patients treated with a TIRF medicine.[14]

[14]Transmucosal immediate release fentanyl (TIRF) medicines REMS modification letter. March 27,2019 https://www.fda.gov/media/122433/download (accessed May 7, 2019)

Market Withdrawal

Market withdrawal of Opana ER

Opana ER (oxymorphone hydrochloride extended-release tablets) was first approved in 2006 for the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The Sponsor reformulated the original product, designed with physicochemical properties intended to make the drug resistant to physical and chemical manipulation for abuse by snorting and injecting. The reformulation was approved in 2011 and the FDA determined that the drug did not meet the Agency's standards to include a description of abuse-deterrent properties in product labeling.

On March 13-14, 2017, an Advisory Committee (AC) meeting was held to discuss the abuse patterns and other safety concerns related to Opana ER. The Agency concluded that reformulated Opana ER was associated with a dangerous shift in the route of abuse from nasal snorting to injection. This was linked to a serious outbreak of HIV and hepatitis C infections in Indiana and multiple cases of thrombotic microangiopathy. The AC voted 18-8 that the benefits of reformulated Opana ER no longer outweigh its risks. In June 2017, the FDA requested that the Sponsor voluntarily remove reformulated Opana ER from the market because the benefits no longer outweighed the risks and the Sponsor complied with the request.[15]

In addition to regulatory actions, FDA can also disseminate information and inform prescribers and other stakeholders of the benefits and risks of opioid products through Drug Safety Communications, press releases, letters to prescribers and published educational materials.

[15] In a case where a company chooses not to remove the product voluntarily, the Agency can take steps to formally require its removal by following the process set forth in FDA regulations to withdraw approval of the marketing application.

Appendix

PAIN MANAGEMENT BEST PRACTICES INTERGENCY TASK FORCE REPORT
UPDATES, GAPS, INCONSISTENCIES, AND RECOMMENDATIONS
DRAFT REPORT April 13, 2019 [16]

EXECUTIVE SUMMARY

Patients with acute and chronic pain in the United States face a crisis due to significant challenges in obtaining adequate care, resulting in profound physical, emotional, and societal cost. According to the CDC, 50 million adults in the United States have chronic daily pain, with 19.6 million adults experiencing high-impact chronic pain that interferes with daily life or work activities. The cost of pain to our nation is estimated at between $565 and $635 billion annually. At the same time, our nation is facing an opioid crisis that, over the past decade, has resulted in an unprecedented wave of overdose deaths associated with prescription opioids, heroin, and synthetic opioids.

The Pain Management Best Practices Inter-Agency Task Force (Task Force) was convened by the US Department of Health and Human Services in conjunction with the Department of Defense (DOD) and the Veterans Administration (VA) with the Office of National Drug Control Policy (ONDCP) to address acute and chronic pain in light of the ongoing opioid crisis. The Task Force mandate is to identify gaps, inconsistencies, and updates, and to make recommendations for best practices for managing acute and chronic pain. The 29 member Task Force included federal agency representatives as well as non-federal experts and representatives from a broad group of stakeholders. The Task Force considered relevant medical and scientific literature and information provided by government and non-government experts in pain management, addiction, mental health and representatives from various disciplines. The Task Force also reviewed and considered patient testimonials and public meeting comments, including approximately 6,000 comments from the public submitted during a 90-day public comment and 3,000 comments from 2 public meetings.

The Task Force emphasizes the importance of individualized **patient-centered care in the diagnosis and treatment of** acute and chronic pain care.

It also emphasizes the development of an effective pain treatment plan after proper evaluation to establish a **diagnosis** with **measurable outcomes that focus on improvements including quality of life (QOL) and functioning**. Achieving excellence in acute and chronic pain care depends on the following:

- An emphasis on an **individualized** patient-centered approach for diagnosis and treatment of pain is essential to establishing a therapeutic alliance between patient and clinician.

- Acute pain can be caused by a variety of different conditions such as trauma, burn, musculoskeletal injury, neural injury, as well as pain due to surgery. A **multi-modal**

[16] https://www.hhs.gov/ash/advisory-committees/pain/meetings/2019-05-09/index.html

approach that includes medications, nerve blocks, physical therapy and other modalities should be considered for acute pain conditions.

- A **multidisciplinary** approach for chronic pain across various disciplines, utilizing one or more treatment modalities, is encouraged when clinically indicated to improve outcomes. These include the following 5 treatment categories:

  - **Medications: Various classes of medications,** including non-opioids and opioids, should be considered for use. The choice of medication should be based on the pain diagnosis, the mechanisms of pain, and related co-morbidities following a thorough history, physical exam, other relevant diagnostic procedures and a **risk-benefit assessment.** The goal is to limit adverse outcomes while ensuring that patients have access to medication-based treatment that can enable a better quality of life and function. Ensuring **safe medication storage** and **appropriate disposal of excess medications** is important to ensure best clinical outcomes and to protect the public health.

    - **Restorative Therapies** including physical therapy, occupational therapy, physiotherapy, therapeutic exercise, and other movement modalities are valuable components of multidisciplinary, multimodal acute and chronic pain care.

    - **Interventional Approaches** including image-guided and minimally invasive procedures are available as diagnostic and therapeutic treatment modalities for acute, acute on chronic, and chronic pain when clinically indicated. A list of various types of procedures including trigger point injections, radiofrequency ablation, cryo-neuroablation, neuro-modulation and other procedures are reviewed.

    - **Behavioral Health Approaches** for psychological, cognitive, emotional, behavioral, and social aspects of pain can have a significant impact on treatment outcomes. Patients with pain and **behavioral health comorbidities** face challenges that can exacerbate painful conditions as well as function, quality of life (QOL), and activities of daily living (ADLs).

    - **Complementary and Integrative Health,** including treatment modalities such as acupuncture, massage, movement therapies (e.g., yoga, tai chi), spirituality, among others, should be considered when clinically indicated.

- Effective multidisciplinary management of the potentially complex aspects of acute and chronic pain should be **based on a biopsychosocial model** of care

- Health systems and clinicians must consider the pain management needs of the **special populations** that are confronted with unique challenges associated with acute and chronic pain, including the following: children/youth, older adults, women, pregnant women, individuals with chronic relapsing pain conditions such as sickle cell disease, racial and ethnic populations, military active-duty service members and Veterans, and cancer and palliative care.

- **Stigma** can be a barrier to treatment of painful conditions. Compassionate, empathetic care centered on a patient-clinician relationship is necessary to legitimize the suffering of

patients with painful conditions and to address the various challenges associated with the stigma of living with pain.

- Improving **education** about pain conditions and their treatment for patients, families, caregivers, clinicians and policy makers is vital to enhancing pain care. Patient education can be emphasized through various means including clinician discussion, informational materials and web resources. More effective education and training about acute and chronic pain should occur at all levels of clinician training, including undergraduate educational curricula, graduate professional training, and continuing professional education, including the use of proven innovations such as the ECHO model. Education for the public as well as for policy-makers and legislators is emphasized to ensure expert and cutting-edge understanding is part of policy that can affect clinical care and outcomes.

- Addressing **access to care** barriers is essential to optimizing pain care. Recommendations include addressing the gap in our **workforce** for all disciplines involved in pain management. Additionally, improved **insurance coverage and payment** for different pain management modalities is a critical component in improving access to effective clinical care, and should including coverage and payment for care coordination, complex opioid management and telemedicine. It is also important to note that in many parts of the country patients will only have access to a primary care provider. Support for education, time and financial resources for PCPs is essential to manage these patients with painful conditions.

- **Research and Development:** Continued medical and scientific research is critical to understanding the **mechanisms underlying the transition from acute to chronic pain**, to translating promising scientific advances into new and effective diagnostic, preventive and therapeutic approaches for patients, and to implementing these approaches effectively in health systems.

A review of CDC Guidelines: (as mandated by the CARA legislation.) The Task Force recognizes the utility of the 2016 Guideline for Prescribing Opioids for Chronic Pain released by the Centers for Disease Control and Prevention (CDC), and its contribution to mitigating unnecessary opioid exposure and the adverse outcomes associated with opioids. It also recognizes unintended consequences that have resulted following the release of the guidelines in 2016, which are due in part to misapplication or misinterpretation of the guideline including forced tapers and patient abandonment. Educating stakeholders about the intent of the guideline (as it relates to the use of opioids for chronic pain by primary care clinicians), reemphasis of the core benefits of the guideline, and encouraging optimal application of this guideline are essential to optimizing acute and chronic pain care. See full section on CDC review in the attached Task Force report.

The Task Force, which included a broad spectrum of stakeholder perspectives, was convened to address one of the greatest public health crises of our time. The Task Force respectfully submits these gaps and recommendations, with special acknowledgement of the brave individuals who have told their stories about the challenges wrought by pain in their lives, the thousands of members and organizations of the public sharing their various perspectives and experiences through public comments, and the millions of others they represent in our nation who have been affected by pain.

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DIVISION OF EPIDEMIOLOGY REVIEW

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Integrated Review of Drug Utilization Data and Epidemiology Literature

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Subject	Prescribing Patterns, Clinical Use, and Risks Associated with Higher Dosage Strength Products and Higher Daily Dosing of Opioid Analgesics

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1. EXECUTIVE SUMMARY

FDA (the Agency) is convening a public Advisory Committee meeting to seek expert and public input on the clinical need for and safety concerns associated with the higher range of opioid analgesic (OA) dosing. The Agency is interested in better understanding current clinical use and situations that may warrant use of higher Daily Doses (DDs, see Appendix A, Glossary of Selected Terms) of OAs as well as the utility of oral or transmucosal Higher Dosage Strength Products (HDSPs, see Appendix A) to meet these needs. We are also interested in discussing the magnitude and frequency of harms associated with the use of higher DDs and HDSPs relative to lower dose therapy, as well as optimal strategies for managing these risks while ensuring access to appropriate pain management for patients.

To inform the Advisory Committee discussion, the FDA Division of Epidemiology II (DEPI) reviewed postmarketing data related to higher DD therapy and the use of HDSPs, including current patterns of use of these drugs and the risks associated with them. Specifically, we aimed to describe the prescribing and current clinical use of HDSPs and to evaluate the evidence from observational studies that examined the risks of abuse, addiction, and overdose associated with higher DDs and HDSPs, relative to lower DDs and Lower Dosage Strength Products (LDSPs, see Appendix A).

FDA's drug utilization analyses focused specifically on oral and transmucosal OAs, comparing use patterns of oral or transmucosal HDSPs to LDSPs and transdermal OAs. HDSPs constituted a very small proportion of overall oral and transmucosal OA utilization. The number of prescriptions dispensed for HDSP decreased at a faster rate than prescriptions dispensed for LDSPs and transdermal OA products from 2013 to 2018. Similarly, a review of published literature revealed that the estimated volume of prescriptions dispensed for higher DD OAs in the U.S. fell substantially from 2006 to 2017, both when expressed as a prescription rate per population and as a percentage of all outpatient retail dispensing of OA prescriptions. Substantial inter-state variability was evident in the rate of higher DD OA prescriptions per population, and this variability also diminished from 2006 to 2017.

In response to FDA inquiries, several large healthcare consortiums reported that the primary clinical needs for HDSPs were to treat patients with cancer, palliative care, or end-of-life care, and that a rare clinical need was to treat patients with severe pain from other complex conditions. The HDSPs were reported as being useful for reducing pill burden, a practical factor that is significant for patients with cancer or at end-of-life, and for dispensing high daily doses of OAs given the limits some payers make on the number of pills they will cover per prescription or per month.

An FDA analysis of the Sentinel Distributed Database (Sentinel), an administrative claims database comprised of commercial and government-funded healthcare insurance claims data from 17 data partners, found that 66% of patients starting HDSPs had claims with diagnoses related to back pain and 66% had claims with diagnoses related to nervous system conditions which included a wide variety of coded diagnoses such as chronic pain syndrome, chronic pain due to trauma, nerve root compression, neuropathies, and other neurological disorders and pain syndromes. Sixty-one percent of patients had claims with diagnoses related to arthritis, and 30% had claims with diagnoses related to cancer (patients may have had more than one diagnostic category claim of interest). Compared to patients starting oral or transmucosal LDSPs, patients starting HDSPs had higher levels of comorbidity based on the modified Charlson Comorbidity

Index,[1] and were also more likely to have claims for mental health conditions and substance use disorders. With respect to demographic and clinical characteristics, patients starting HDSPs appeared fairly similar to patients starting transdermal OA products.

The epidemiologic literature on risks associated with higher dose OAs focused on total average DD, and none of the studies reviewed compared the risks of abuse, addiction, and overdose among patients prescribed HDSPs, relative to patients prescribed LDSPs. Limited epidemiologic evidence from published healthcare claims-based studies suggests an association between higher prescribed DD and increased risks of abuse and addiction. However, due to the limitations of healthcare data, including the difficulty establishing temporal relationships, it remains unclear whether the higher dose plays a causal role in the development of opioid addiction. To more fully understand this relationship, additional evidence is needed from prospective epidemiologic studies and other research disciplines.

The epidemiologic evidence suggests that higher DD of OAs likely contributes causally to increased risk of intentional and unintentional opioid overdose, although DD is only one of multiple, important factors influencing overdose risk. The association between DD and overdose risk appears to be linear, with no threshold value for prescribed DD that discriminates well between patients who will versus will not go on to have an overdose, and a substantial proportion of prescription opioid overdoses occur among patients prescribed lower DDs or with no OA prescription on record at all.

2. INTRODUCTION

FDA is seeking expert and public input on the clinical need for and safety concerns associated with the higher range of OA dosing. The Agency is interested in better understanding current clinical use and situations that may warrant use of higher doses of OAs and the utility of HDSPs to meet these needs. We are also interested in discussing the magnitude and frequency of harms associated with higher dose OA therapy relative to lower dose therapy, as well as optimal strategies for managing these risks while ensuring access to appropriate pain management for patients.

To better understand both the clinical utility and harms of higher dose OAs in the current environment, and to discuss the advantages and disadvantages of various potential risk management strategies, FDA is bringing these issues to an advisory committee to seek input and advice from the clinical, patient, public health, and research communities.

To inform the advisory committee discussion, the FDA Division of Epidemiology II (DEPI) reviewed postmarketing data related to higher DD therapy and the use of HDSPs, including current patterns of use of these drugs and the risks associated with them. Specifically, we aimed to describe the prescribing patterns and clinical use of HDSPs and to evaluate the evidence from observational studies that examined the risks of abuse, addiction, and overdose associated with higher DDs and HDSPs, relative to lower DDs and LDSPs.

3. REVIEW METHODS AND MATERIALS

3.1. Key concepts

A key element in examining dosage strength across OA products is the relative potency across different opioid moieties. One of the most commonly used methods for standardizing dose across different OA moieties is converting to morphine milligram equivalents (MME), often available as MME conversion tables.

However, there is variability between published MME conversion tables depending upon the resource used. Data underlying many published MME conversion tables come from studies of varying completeness, quality, and generalizability. For example, some of these were single dose studies,[2] that measured only analgesic effects (i.e., not respiratory depression or euphoric effects) in very small study populations that may not be more broadly representative to individuals with varying levels of opioid tolerance.[3-6] For this review, we calculated MMEs based upon currently available published sources.[q] However, we acknowledge that MME is an evolving science and do not endorse any particular definition or table of published values.

Another key challenge involves defining high versus low daily dose or dosage strength, as there is no standard threshold value that defines high versus low dose OAs. Products exist along a range of dosage strengths in both immediate- and extended-release formulations, and these are sometimes combined or prescribed for "as needed" use without a regular dosing schedule. In analyses conducted by FDA, we defined HDSPs in two different ways, as described below in Sections 3.3.1 and 3.3.2. The literature reviewed also used varied definitions for high DD, and these definitions are included in the study summary tables (Appendix E and F).

3.2. Review outline

As described in further detail in Section 3.3, this review focused on three main topic areas:

1. ***Quantifying higher dose OA prescribing in the United States*:**
   - FDA drug utilization data analyses of national estimates for HDSP and LDSP prescriptions and units (e.g. tablets) dispensed from U.S. pharmacies, and patients who received these prescriptions
   - Review of published studies of national estimates of higher DD OA prescriptions dispensed from U.S. pharmacies
2. ***Clinical use of higher dose OAs*:**
   - Responses to an FDA scientific inquiry of selected health systems, describing perceived clinical needs for HDSPs and any restrictions on higher dose OA prescribing

[q] In this review we used the following references to determine conversion factors for calculating morphine milligram equivalents: National Center for Injury Prevention and Control, https://www.cdc.gov/drugoverdose/media/; McPherson, ML. Demysifying Opioid Conversion Calculations, published by ASHP.; Medscape https://emedicine medscape.com/article/2138678-overview; Centers for Medicare and Medicaid Services; GlobalRPh website, http://globalrph.com/narcoticonv.htm.

- FDA analyses of Sentinel data describing the clinical and demographic characteristics and use patterns of patients who received HDSPs compared to patients who received LDSPs or transdermal OA products
- Review of published studies describing the clinical and demographic characteristics of patients who received higher DD OAs compared to patients who received lower DD OAs

3. ***Review of the epidemiologic literature on the associations between higher dose OAs and the risks of abuse, addiction, and overdose***

- Review of published studies examining the association between prescribed OA DD and risks of abuse or addiction
- Review of published studies examining the association between prescribed OA DD and risk of unintentional or intentional fatal or nonfatal overdose

3.3. Description of methods

3.3.1. Quantifying higher dose OA prescribing in the U.S.

3.3.1.1. FDA analysis of the estimated number of prescriptions and patients in the U.S. who received HDSPs, LDSPs and transdermal OAs

We used the IQVIA National Prescription Audit™ data source, a proprietary drug utilization database available to the FDA, to obtain the nationally estimated numbers of units (e.g. tablets, lozenges) and prescriptions for oral, transmucosal and transdermal opioid products labeled for analgesia dispensed to patients from U.S. outpatient retail pharmacies from 2013-2018, annually (see Appendix B for a detailed database description). We further stratified these data by product dosage strength, calculated as MME per each single unit (e.g. MME per one tablet). For selected analyses, we stratified results as oral or transmucosal products with ≥ 90 MME per unit compared to those with < 90 MME per unit to categorize products as HDSPs or LDSPs. This was an arbitrary threshold used to dichotomize the distribution of dosage strength per unit among dispensed prescriptions. Analyses comparing use patterns for HDPS and LDSPs focused on oral and transmucosal OAs, such as tablets, liquids, lozenges, and films. Transdermal OA products were included as a comparator group to assess how their use was similar to or different from the use of HDSPs. Data were also stratified by immediate-release (IR) and extended-release or long-acting (ER/LA) dosage formulations.

We used the IQVIA Total Patient Tracker™ data source, a proprietary drug utilization database available to FDA, to obtain the nationally estimated numbers of patients with dispensed prescriptions for oral, transmucosal, or transdermal opioid products labeled for analgesia from U.S. outpatient retail pharmacies from 2013-2018, annually (see Appendix B). Again, for selected analyses we stratified these patient data by oral or transmucosal products with ≥ 90 MME per unit compared to products with < 90 MME per unit to obtain estimates of patients who were dispensed prescriptions for oral or transmucosal HDSPs and LDSPs, with transdermal OA products as a comparator group.

3.3.1.2. Review of published studies of national estimates of higher DD OA prescriptions dispensed from U.S. pharmacies

We also reviewed and summarized relevant findings from two published studies that described:

- National patterns and trends in the prescription volume of higher DD OAs, defined as an OA prescription with an average DD ≥90 MME/day, dispensed from U.S. pharmacies in 2006-2017[7]
- The distribution of DD (from one prescription or multiple, concurrent prescriptions) among the population dispensed OAs in North Carolina in 2010[8]

3.3.2. Clinical use of higher dose OAs

3.3.2.1. Selected health systems' descriptions of perceived clinical needs for HDSPs and restrictions on higher dose OA prescribing

Leveraging FDA's contractual relationships with several healthcare delivery and payer organizations, we sought qualitative information on the perceived clinical need for and policies around prescribing HDSPs. In August, a scientific inquiry was sent to the four healthcare organizations that hold contracts for the FDA Pharmacoepidemiology Research Program. Again, because of widespread familiarity with the 2016 CDC guidelines,[9] we used 90 MME/day as a benchmark for higher dosage strength product prescribing, defining HDSPs as those OA *products* likely to be associated with DDs above this level. Specifically, in our inquiries, we defined the salient category of OAs as "*all products and product strengths of oral or transmucosal opioid analgesic products for which taking a single unit dose (e.g., tablet, capsule) at the minimum recommended dosing interval would result in a total daily dose of greater than 90 morphine milligram equivalents (MMEs).*"

The inquiry included the following questions:

- *What is the perceived clinical need for these products and rationale for inclusion in formulary?*
- *What restrictions, if any, have been placed on prescribing of these products?*
- *If restrictions have been implemented, we request information on the following:*
    - *Any exceptions that are in place to these restrictions,*
    - *The one or two most important reasons for the restrictions,*
    - *The reactions to these policies from providers and patients,*
    - *The measured outcome(s) of these policies, if any.*

In Section 4.1.2, we summarize the responses received, noting areas of agreement and disagreement among the responding organizations.

3.3.2.2. FDA analysis of the clinical and demographic characteristics and use patterns of patients who received HDSPs compared to patients who received LDSPs or transdermal OA products

We conducted an analysis of oral, transmucosal, and transdermal OAs using the Sentinel Distributed Database (Sentinel, see Appendix B)[10] from January 2012 through June 2018. Seventeen data partners[r] contributed data, with individual data start and end dates varying among the data partners. Public insurance sources (e.g., Medicare) provided data from 2012-2016. This data source included 100% of the Medicare Fee-for-Service population. Therefore, patients aged 65 years or older were overrepresented due to a more comprehensive capture of Medicare claims than other insurance types. The remaining patients in the data source were largely commercially-insured patients. The sample did not include patients without health care insurance or those enrolled in health care plans not included in the Sentinel data source.

Within the Sentinel data, which is primarily based on administrative claims data, we identified patients with pharmacy claims for oral or transmucosal OAs. We also included patients with pharmacy claims for transdermal OAs as a comparator group. Again, analyses comparing use of HDSPs and LDSPs focused on oral and transmucosal OAs. Transdermal OAs were included as a comparator group.

For this analysis, we defined HDSPs as oral or transmucosal OAs which, when one unit (e.g. tablet, lozenge) is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result in a total daily dose of ≥ 90 MME. Similarly, we defined LDSPs as oral or transmucosal OAs which, when one unit is taken at the lowest frequency according to the FDA-approved label, would result in a total daily dose of < 90 MME. For example, the labeled usual adult dosage for hydrocodone/acetaminophen 5 mg/325 mg is 1-2 tablets every 4-6 hours as needed for pain.[11] We calculated the MME daily dose based on the lowest around the clock frequency as 1 tablet dosed every 6 hours—20 MME per day in this example if using an MME conversion factor of 1. An example of an HDSP would be oxycodone extended-release 40 mg tablets, dosed every 12 hours according to the FDA-approved label,[12] would be 120 MME per day using an MME conversion factor of 1.5. Again, we chose a daily dose of 90 MME as an arbitrary threshold to dichotomize our analysis because this daily dose is commonly used in some OA prescribing guidelines[9] as a marker of higher dose OA regimens. Table C1 in Appendix C provides details of the products included in the analysis: oral or transmucosal OAs, categorized as HDSPs versus LDSPs, as well as transdermal OAs (regardless of dosage strength).

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[r] Data Partners who provided used in the analysis: Aetna, Blue Bell, PA; Blue Cross Blue Shield of Massachusetts, Boston, MA; Duke University School of Medicine, Department of Population Health Sciences, Durham, NC, through the Centers for Medicare and Medicaid Services which provided data; Harvard Pilgrim Health Care Institute, Boston, MA; HealthCore, Inc., Translational Research for Affordability and Quality, Alexandria, VA; HealthPartners Institute, Minneapolis, Minnesota; Humana, Inc., Healthcare Research, Miramar, FL; Kaiser Permanente Colorado Institute for Health Research, Denver, CO; Kaiser Permanente Center for Health Research Hawai'i, Honolulu, HI; Kaiser Permanente Mid-Atlantic States, Mid-Atlantic Permanente Research Institute, Rockville, MD; Kaiser Permanente Northern California, Division of Research, Oakland, CA; Kaiser Permanente Northwest Center for Health Research, Portland, OR; Kaiser Permanente Washington Health Research Institute, Seattle, WA; Marshfield Clinic Research Institute, Marshfield, WI; Meyers Primary Care Institute, Worcester, MA; OptumInsight Life Sciences Inc., Boston, MA; Vanderbilt University Medical Center, Department of Health Policy, Nashville, TN, through the Tennessee Division of TennCare of the Department of Finance and Administration which provided data.

We then examined various characteristics of patients who received HDSPs, LDSPs, or transdermal OAs. To examine pain-related diagnoses and other medical conditions temporally associated with receiving OAs in each of the three categories, we evaluated all patients with six months of eligibility prior to their first pharmacy claims for an HDSP, LDSP, or transdermal OA. In these patients, we searched for claims with diagnoses or procedures of interest from six months before though one month after their first dispensing for a drug in the category. Pain-related conditions were defined and operationalized using the Clinical Classifications Software for International Classification of Diseases versions 9 and 10 (ICD-9-CM, ICD-10-CM) published by the Health Cost and Utilization Project.[13] We used National Drug Codes and Healthcare Common Procedure Coding System (HCPCS) codes to identify drugs and selected conditions of interest. We calculated a modified Charlson Comorbidity Index[1] (CCI) for patients receiving drugs in each of the three categories, again using claims in the six months before through one month after the first dispensing of a drug in that category.

Among patients starting a drug in each OA product category, we examined the average cumulative length of therapy for that OA product category. 'Starting therapy' was defined as an incident claim for a drug in an OA product category, e.g. an incident claim for an HDSP, with no claims for an HDSP in the 6 months prior.

For each pharmacy claim for an HDSP, LDSP, or transdermal OA, we evaluated concomitant use of benzodiazepines, gabapentinoids (gabapentin or pregabalin), or selected sedatives commonly referred to as 'Z-drugs' (eszopiclone, zaleplon, or zolpidem). Concomitant use was defined as a pharmacy claim for a drug of interest in the seven days prior to, the day of, or up to seven days after the pharmacy claim for the OA. Table C2 in Appendix C describes the products included in the concomitant use analysis.

3.3.2.3 Review of published studies describing the clinical and demographic characteristics of patients who received higher DD OAs

We also sought data on clinical and demographic characteristics of patients who received higher DD OA therapy, as ancillary information to our analysis of HDSPs in the Sentinel data. We used the published papers we identified in our search for epidemiologic studies of the associations between OA dose and the risks of abuse, addiction, and overdose. (Section 3.3.3 describes the literature search methods.) We abstracted each paper's data on the distributions of clinical and demographic characteristics of patients on higher DD OA therapy, noting the paper's definition of higher DD.

3.3.3. Review of the epidemiologic literature on the associations between higher dose and the risks of abuse, addiction, and overdose

We conducted a literature review of published epidemiologic studies examining the risks of abuse, addiction, and overdose associated with higher OA DD, relative to lower OA DD, or risks associated with HDSPs, relative to LDSPs. Using the following procedure, we identified peer-reviewed, English-language articles that reported results from epidemiologic studies with a cohort or case-control design:

1) We searched PubMed for publications that had been entered from 01/01/2009-12/31/2018 (Appendix D contains the search strategy) and reviewed the resulting article titles to determine whether further review of the article was likely to be relevant.

2) We reviewed abstracts for titles that appeared to be related to the topic.
3) If the abstract suggested that the article reported results from a cohort or case-control study of the association of higher doses of OAs with the risk of abuse, addiction, and overdose, we reviewed the full text.
4) We evaluated the validity of the results qualitatively, considering the potential for bias, confounding, misclassification, and random error to affect the study results.

4. REVIEW RESULTS

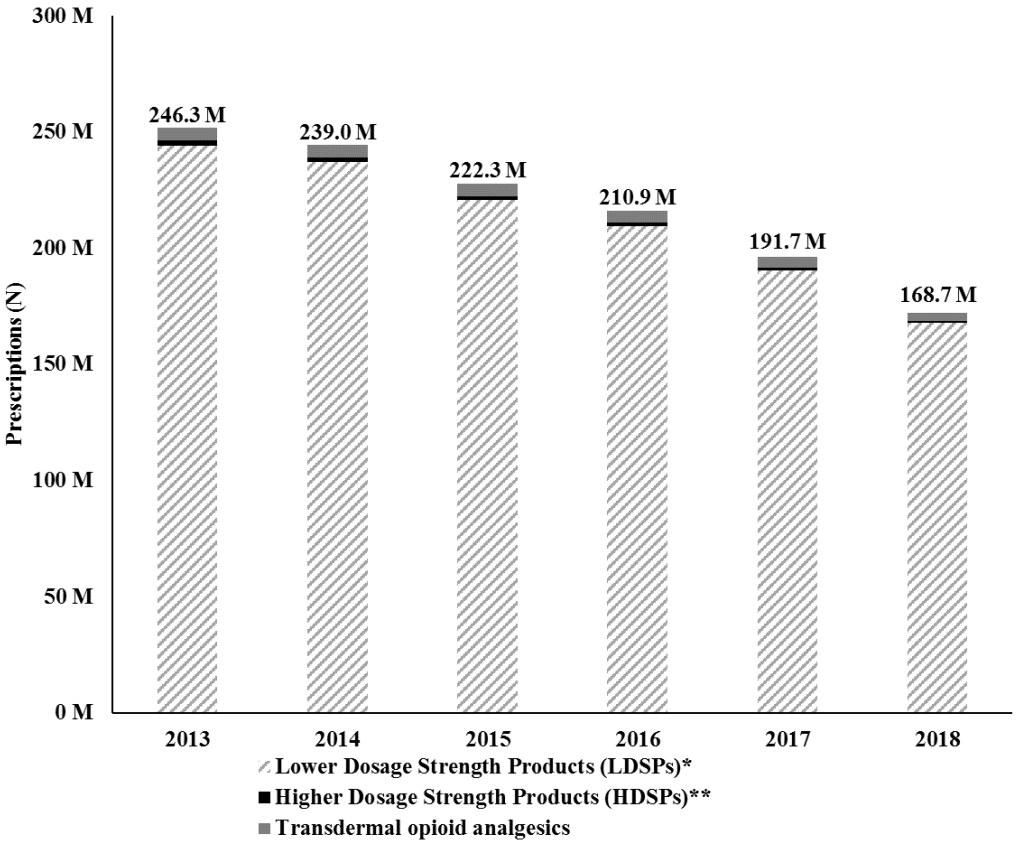
4.1. Quantifying higher dose OA prescribing in the United States

4.1.1. Estimated number of prescriptions and patients in the U.S. receiving HDSPs, LDSPs, and transdermal OAs

4.1.1.1 FDA analysis of HDSPs, LDSPs, and transdermal OA prescriptions dispensed in the U.S.

In 2018, an estimated 168.7 million prescriptions for oral or transmucosal OAs were dispensed in the U.S. (Figure 1 below), a 32% decrease from 246.3 million prescriptions in 2013. Annually from 2013 to 2018, 1% or less of prescriptions for all oral or transmucosal formulations were for HDSPs, **defined in this analysis as an oral or transmucosal OA where one unit (e.g. tablet, lozenge) is ≥ 90 MME**, and 99% or more were for LDSPs (Table C3 in Appendix C). Prescriptions for HDSPs decreased 63%, from 2.2 million prescriptions in 2013 to 0.8 million prescriptions in 2018. During the same time frame, prescriptions for LDSPs decreased 31%, and prescriptions for transdermal OAs (regardless of dosage strength) decreased 34%. Extended-release or long-acting products comprised over 97% of annual HDSP prescriptions dispensed from 2013 to 2018.

Figure 1. Nationally estimated number of higher and lower dosage strength oral, transmucosal, or transdermal OA prescriptions dispensed from U.S. outpatient retail pharmacies, 2013 - 2018.



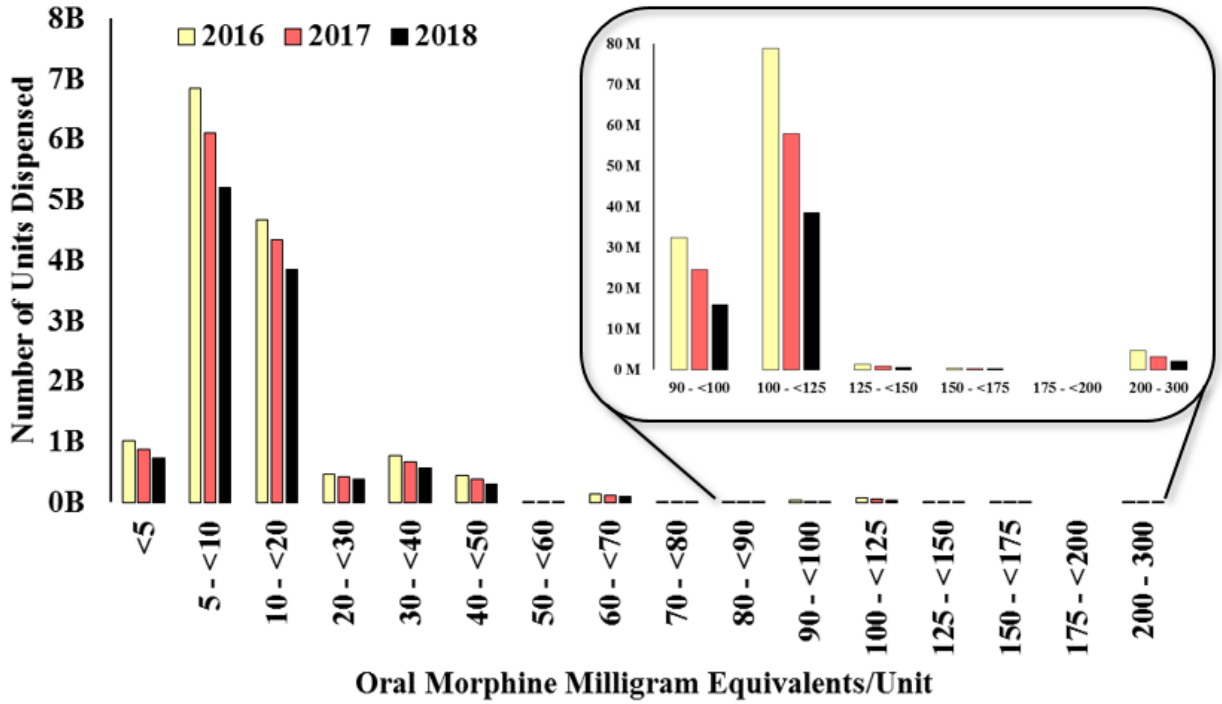
Source: IQVIA National Prescription Audit™. Data years 2013-2018. Data extracted January 2019
MME was calculated using published conversion factors for each product, dosage form, and strength.
* Lower Dosage Strength Products (LDSPs) are oral or transmucosal OA products for which one unit (e.g. tablet, lozenge) is < 90 MME
** Higher Dosage Strength Products (HDSPs) are oral or transmucosal OA products for which one unit is ≥ 90 MME

4.1.1.2 FDA analysis of dispensed OAs units in the U.S., by dosage strength

An estimated 11.2 billion oral or transmucosal OA units (e.g. tablets, lozenges) were dispensed in 2018, a 23% decrease from 2016 (14.4 billion units) and a 33% decrease from 2013 (16.7 billion units, Table C3 in Appendix C). In 2018, approximately 58 million HDSP units were dispensed, a 34% decrease from 2017 (87 million units), a 51% decrease from 2016 (118 million units), and a 67% decrease from 2013 (173 million units). Extended-release or long-acting products comprised over 96% of HDSP annual units dispensed from 2013 to 2018.

In 2018, an estimated 88% of dispensed oral or transmucosal OA dispensed units were for products with <20 MME per unit; 12% were for products with 20-89 MME per unit, and less than 1% were for products with ≥90 MME per unit (Figure 2 below). A decrease was seen in the number of units dispensed for all dosage strength categories from 2016 to 2018.

Figure 2. Nationally estimated number of oral or transmucosal OA units*, by oral morphine milligram equivalents (MME) per unit, dispensed from U.S. outpatient retail pharmacies, 2016 - 2018.

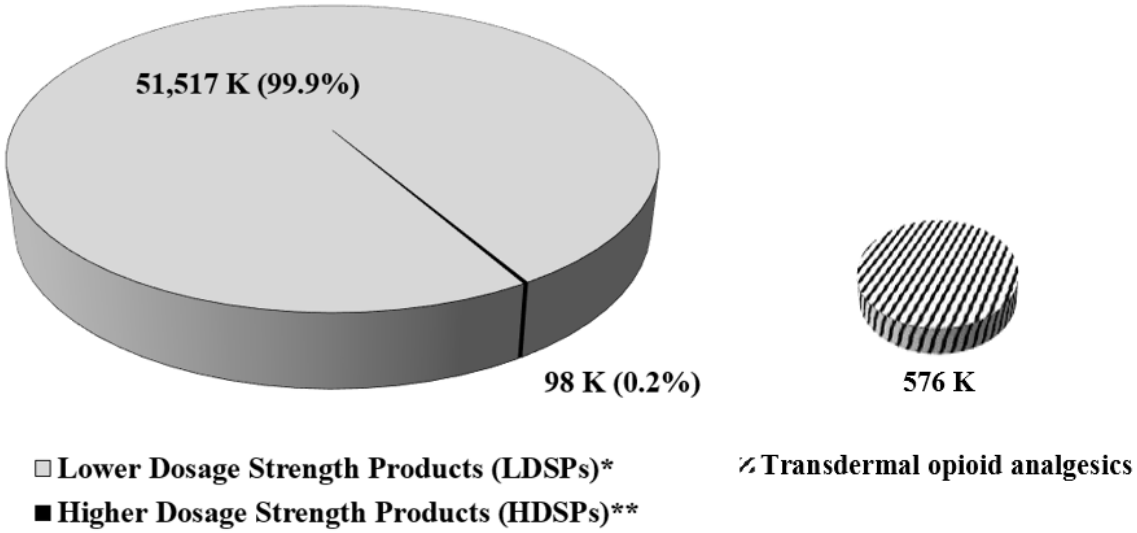


Source: IQVIA National Prescription Audit™. Data years 2016-2018. Data extracted January 2019
MME was calculated using published conversion factors for each product, dosage form, and strength.
* Units represented one single dosage unit, such as one tablet or one lozenge.

4.1.1.3 FDA analysis of the number of patients dispensed HDSP, LDSP, and transdermal OA prescriptions in the U.S.

In 2018, approximately 51.6 million patients were dispensed prescriptions for oral or transmucosal OAs (Figure 3 below, Table C4 in Appendix C). Of these patients, approximately 98,000 patients (0.2%) received HDSP prescriptions in 2018, compared to 51.5 million patients (99.9%) who received LDSP prescriptions. Some patients may have received more than one type of OA in a given year, and therefore patient counts may sum to more than the total. By comparison, approximately 576,000 patients were dispensed a prescription for a transdermal OA in 2018. The number of patients with dispensed prescriptions for HDSPs decreased 67% from 2013 to 2018, and the number of patients with dispensed prescriptions for LDSPs decreased 26% during the same time frame (data not shown).

Figure 3. Nationally estimated number of patients dispensed prescriptions for higher and lower dosage strength oral or transmucosal OAs and transdermal OAs from U.S. outpatient retail pharmacies in 2018.



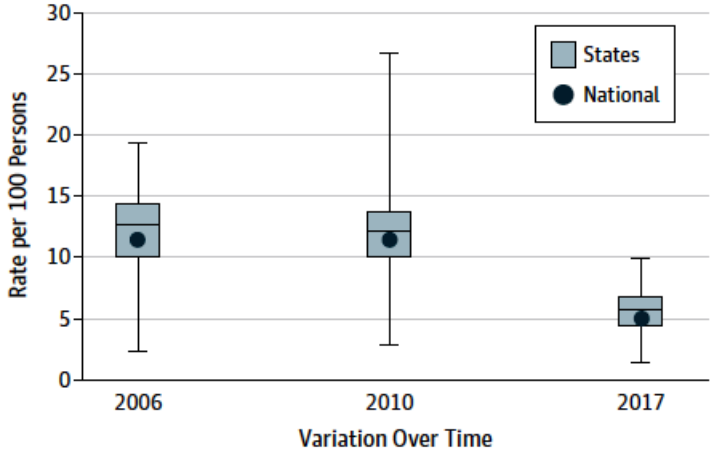
Source: IQVIA Total Patient Tracker™. 2013-2018, Data extracted January 2019.
MME was calculated using published conversion factors for each opioid molecule, dosage form, and product.
* Lower Dosage Strength Products (LDSPs) are oral or transmucosal OA products for which one unit (e.g. tablet, lozenge) is < 90 MME
** Higher Dosage Strength Products (HDSPs) are oral or transmucosal OA products for which one unit is ≥ 90 MME

4.1.2 Review of published studies of the estimated number of prescriptions for higher DD OAs

Nationally, from 2006 to 2017, the estimated rate of higher DD OA prescriptions fell 53%, from 11.5 to 5.0 per 100 persons (higher dose defined here as ≥90 MME per day).[7] After remaining stable from 2006-2009, this rate declined from 2009-2017 by an average of 9.5% per year.[7] Within each year, the rate of higher DD OA prescriptions varied substantially by state, as indicated by the distributions depicted by box and whisker plots in Figure 4. This inter-state variation also appeared to decline from 2006-2017 (Figure 4).

Overall OA use increased from 2006-2012, then declined from 2012-2017.[7] The percentage of all OA prescriptions that were higher DD prescriptions declined every year, from 15.8% in 2006 to 8.5% in 2017.[7]

Figure 4. Rates per 100 Persons of OAs Prescribed in Daily Dose ≥90 MME, in 2006, 2010, and 2017: United States, IQVIA Xponent Database.

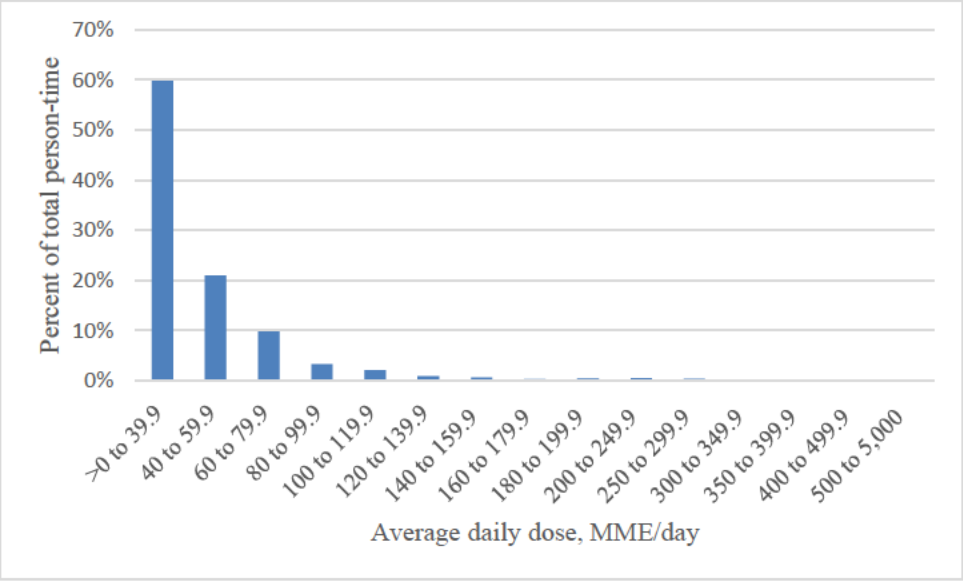


	2006	2010	2017
PERCENT OF ALL OA PRESCRIPTIONS WITH DAILY DOSE ≥90 MME	15.8	14.0	8.5

Source: Scheiber et al. 2019,[7] Figure 3A and Table 1. Rates of OAs prescribed in daily dose ≥90 MME were determined from all opioids for each state and the District of Columbia in that year.

We found few studies that examined how average DD is distributed among a general population of patients who receive OAs. One study analyzed North Carolina Prescription Drug Monitoring Program (PDMP) records of OA prescriptions dispensed in the state in 2010 to show the distribution of person-time by relatively fine categories of average DD, which was calculated for each person, summing across multiple, concurrent prescriptions if applicable.[8] Figure 5 shows each DD category's percent of the total exposed person-years among NC residents in 2010. Ninety-four percent of person-time was exposed to <100 MME/day. (Ninety MME/day was not a cut-point in this paper's analyses.)

Figure 5. Distribution of exposed person-time by average daily dose* (MME/day) of dispensed OA: North Carolina residents (N=2,182,374), State Prescription Drug Monitoring Program, 2010.



Source: FDA-prepared figure of data published in Dasgupta, et al. (2016) Table 1.[8]
*Average daily dose was calculated by the total MME dispensed in the prescription, divided by the days' supply, and incorporated overlapping prescriptions dispensed to an individual. The days' supply was used to calculate person-time in each category.

4.2. Clinical use of higher dose OAs

4.2.1 Selected health systems' perceived clinical needs for HDSPs and restrictions on higher dose OA prescribing

In September and October 2018, FDA received three responses to our inquiry regarding the current clinical use and need for higher dosage strength OA products and experiences with efforts to reduce higher dose OA prescribing in various healthcare settings:

- Brigham and Women's Hospital (Boston, MA) conducted interviews with four pain management experts within the Partners HealthCare System, located in Boston and nearby communities.
- Harvard Pilgrim Health Care (Boston, MA) conveyed the questions to the Health Care Systems Research Network (HCSRN), which is composed of organizations across the U.S., and summarized responses from the various member organizations.
- HealthCore, Incorporated (Wilmington, DE) answered the questions based on what it had learned from prior analyses of its HealthCore Integrated Research Database, a large administrative database of healthcare claims, and from experience implementing policies to restrict prescribing higher doses of OAs.

4.2.1.1 Perceived clinical need for these products and rationale for inclusion in formulary

All respondents identified the clinical needs for higher dosage strength OA products as treating pain in patients with:

- Cancer

- Terminal illness in need of palliative or hospice care
- More rarely, complex chronic conditions, e.g., sickle cell disease, often with high comorbidity

The higher dosage strength products were reported as being useful for:

- Reducing pill burden, a practical factor that is important for patients with cancer or at end-of-life
- Dispensing high daily doses of OAs given the limits some payers make on the number of pills they will cover per prescription or per month

4.2.1.2 Current restrictions on prescribing HDSPs

When asked what restrictions had been imposed on prescribing, all respondents indicated that states, payers, or both, had placed limits on the amount of OAs prescribed. While these restrictions were not product-specific, many of them affected prescriptions for higher daily OA doses. Restrictions identified were:

- Extended-release OAs were covered only after immediate-release OAs had been tried
- Other limits on what was covered by insurance, including
    - Number of pills per prescription or per month
    - Daily dose, MME, e.g., ≤90 MME
    - Number of days' supply

Notably, some of the indications identified as the primary clinical needs for HDSPs, i.e., treating pain in patients with cancer or at end-of-life, were excepted from these restrictions. Prescribers could also seek other exceptions through prior authorization procedures for patients with severe, chronic pain related to other conditions.

When asked about the reactions to these restrictions from providers and patients, responses were mixed. Two respondents reported that patients and providers generally understood and accepted the changes in OA prescribing, owing to their awareness of the opioid abuse crisis. The third respondent had a more ambivalent perspective. On the one hand, the restrictions were helpful for engaging chronic pain patients in discussing opioid dose reduction. On the other hand, cancer patients and their providers could be frustrated by the additional steps needed to obtain coverage for the high doses needed for pain relief. In some cases, physicians had responded to these restrictions by initiating opioid tapers or even dropping patients, and this raised concerns about patients seeking opioids "from the street."

The measured outcomes of these policies included changes in prescribing practices: prescribing of all OAs, and of opioids in high doses, had declined in the past several years, consistent with national trends. There were no data concerning the impact of these policies on patient health. However, in the HCSRN, some regions of Kaiser Permanente were participating in a related research effort, The Program for Active Coping and Training, described as "a large, pragmatic trial testing the effectiveness of integrating an evidence-based, interdisciplinary pain management intervention for chronic pain patients."

4.2.2 FDA analysis of Sentinel data: clinical and demographic characteristics and use patterns of patients who received HDSPs, LDSPs, and transdermal OA products

Between January 2012 and June 2018, data for 149,132,305 eligible members in the Sentinel data were evaluated for one or more claims for an OA over a total of 368,276,832 eligible member-years. Of these members, 47,416,985 members (32%) had at least one pharmacy claim for an oral or transmucosal OA (Table 1 below). Approximately 4% (1.8 million) of patients with an oral or transmucosal OA claim had at least one claim for an HDSP, **defined in this analysis as an oral or transmucosal OA which, when one unit (e.g. tablet, lozenge) is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result in a total daily dose of 90 MME or greater.** Over 99% of patients (47.2 million patients) with an oral or transmucosal OA claim had at least one claim for an LDSP. Three percent (1.6 million) of patients with claims for oral or transmucosal OAs had claims for both HDSPs and LDSPs. By comparison, 1.3 million patients had at least one claim for a transdermal OA product.

4.2.2.1 Patient demographics

Fifty-seven percent of patients with a claim for either an HDSP or an LDSP were female, compared to 65% for those with transdermal OA claims (Table 1 below). In this sample, the mean age of patients at the time of an HDSP claim was 57 years, compared to 61 years for patients with an LDSP claim and 67 years for patients with a transdermal OA claim. Our sample included 100% of the Medicare Fee-for-Service population. Therefore, patients aged 65 years or older were overrepresented in the patient sample due to a more comprehensive capture of Medicare claims than other insurer claims. Observed age distributions in this analysis may differ from nationally representative age distributions of patients receiving OAs.

Table 1. Demographic characteristics of patients with claims in the Sentinel Distributed Database for higher and lower dosage strength oral or transmucosal OAs and transdermal OAs, January 2012 through June 2018.

	Any oral or transmucosal opioid analgesic*	Lower dosage strength products (LDSPs)**	Higher dosage strength products (HDSPs)***	Transdermal opioid analgesics
Unique patients	47,416,985	47,178,068	1,844,419	1,293,201
Female (%)	57%	57%	55%	65%
Pharmacy claims†	373,466,910	350,546,610	27,349,071	13,802,509
Mean age (years)‡	61	61	57	67
<18 years old	1%	1%	<1%	<1%
18-29 years old	4%	4%	2%	1%
30-49 years old	20%	19%	26%	14%
50-64 years old	31%	30%	47%	30%
65+ years old	45%	46%	25%	55%

Source: Sentinel Distributed Database, January 2012-June 2018. This data includes 100% of the Medicare Fee-for-Service population from 2012 through 2016. Therefore, age distributions in this analysis may differ from nationally representative age distributions of patients receiving OAs with an overrepresentation of patients aged 65 years or older.

* Totals may sum to more than the total of lower and higher dosage strength products because patients may have had both a lower and higher dosage strength OA claim within one calendar year.

** Lower dosage strength products (LDSPs) were defined in this analysis as oral or transmucosal OA products which, when one unit (e.g. tablet, lozenge) is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result a total daily dose of < 90 MME.

*** Higher dosage strength products (HDSPs) were defined in this analysis as oral or transmucosal OA products which, when one unit is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result a daily dose of ≥ 90 MME.

† Multiple pharmacy claims for a particular OA on the same day for a patient were de-duplicated into only one claim

‡ Mean age at time of each prescription claim

4.2.2.2 Pain-related diagnoses

Among patients who started HDSPs, 66% of patients also had claims associated with back pain and related back conditions, 66% had claims related to other nervous system conditions, 61% had claims related to arthritis and nontraumatic joint conditions, and 30% had claims related to cancer (Table 2 below). Patients had claims related to multiple diagnoses of interest, and therefore percentages for pain-related conditions add to more than 100%. The results for patients who started HDSPs were similar to those for patients who started transdermal OAs. Among patients who started LDSPs, the proportions of patients with claims related to these diagnoses were lower—37% had claims related to arthritis and nontraumatic joint conditions, 30% had claims associated with back pain and related back conditions, 22% had claims related to other nervous system conditions, and 16% had claims related to cancer. The proportions of patients with claims for trauma/injury/fracture/burns or sprain/strain/contusions (21-24%) were similar for patients who started HDSPs or transdermal OAs and were slightly higher than patients who started LDSPs (16-17%).

4.2.2.3 Comorbidities

The modified Charlson Comorbidity Index (CCI) was higher for patients who started HDSPs (CCI=3.2) or transdermal OAs (CCI=3.9) compared to patients who started LDSPs (CCI=0.9, Table 2 below). Fifty-four percent of patients who started HDSPs and 55% who started transdermal OAs had a claim with a diagnosis or procedure related to mental health, compared to 23% for patients who started LDSPs. Nine percent of patients who started HDSPs had a claim with a diagnosis or procedure related to substance use disorder, compared to 7% for patients who started transdermal OAs and 2% for LDSPs.

Table 2. Clinical characteristics of patients in the Sentinel Distributed Database with claims for higher and lower dosage strength oral or transmucosal OAs and transdermal OAs, January 2012 through June 2018.

	Any oral or transmucosal opioid analgesic*		Lower dosage strength product (LDSP)**		Higher dosage strength product (HDSP) ***		Transdermal opioid analgesic	
	N/mean	%/SD	N/mean	%/SD	N/mean	%/SD	N/mean	%/SD
Number of unique patients (N)	**34,634,159**		**34,797,803**		**1,013,649**		**845,643**	
Pain-related conditions†								
Back Pain & Back Conditions	10,146,356	29%	10,327,816	30%	673,432	66%	617,720	73%
Other Nervous System Condition	7,543,170	22%	7,683,214	22%	665,988	66%	594,803	70%
Arthritis & Nontraumatic Joint Conditions	12,677,827	37%	12,798,662	37%	616,856	61%	575,668	68%
Abdominal Pain	5,851,972	17%	5,904,333	17%	308,511	30%	296,025	35%
Cancer	5,504,091	16%	5,532,416	16%	306,315	30%	320,498	38%
Trauma, Injury, Fracture, & Burns	5,593,952	16%	5,631,571	16%	245,829	24%	241,430	29%
Sprains, Strains, & Contusions	5,986,627	17%	6,025,315	17%	210,854	21%	183,900	22%
Headache, Including Migraine	3,073,496	9%	3,114,847	9%	181,558	18%	154056	18%
Sickle Cell Anemia	31,356	<1%	32,712	<1%	5,044	1%	2314	<1%
Clinical conditions†								
Modified Charlson Comorbidity Index‡	0.9	2	0.9	2	3.2	3.6	3.8	3.9
Mental Health	7,839,552	23%	7,945,088	23%	547,586	54%	463,779	55%
Substance Use Disorder	666,810	2%	692,415	2%	85,877	9%	59,259	7%

Source: Sentinel Distributed Database, January 2012-June 2018. This data includes the 100% Medicare Fee-for-Service population from 2012 through 2016 and therefore age distributions in this analysis may differ from nationally representative age distributions of patients receiving OAs, with an overrepresentation of patients aged 65 years or older.

* Totals may sum to more than the total of lower and higher dosage strength products because patients may have had both a lower and higher dosage strength OA claim within one calendar year.

** Lower dosage strength products (LDSPs) were defined in this analysis as oral or transmucosal OA products which, when one unit (e.g. tablet, lozenge) is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result a total daily dose of < 90 MME.

*** Higher dosage strength products (HDSPs) were defined in this analysis as oral or transmucosal OA products which, when one unit is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result a daily dose of ≥ 90 MME.

† Pain-related conditions and clinical conditions were assessed for the 183 days prior to, day of, and 30 days following a patient's initial observed claim for an oral, transmucosal, or transdermal OA. Pain-related conditions may add to more than 100% due to patients having claims for more than one condition or diagnosis of interest. Pain-related conditions were categorized using the Clinical Classifications Software for ICD-9-CM and ICD-10-CM published by the Health Cost and Utilization Project, available at https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp.

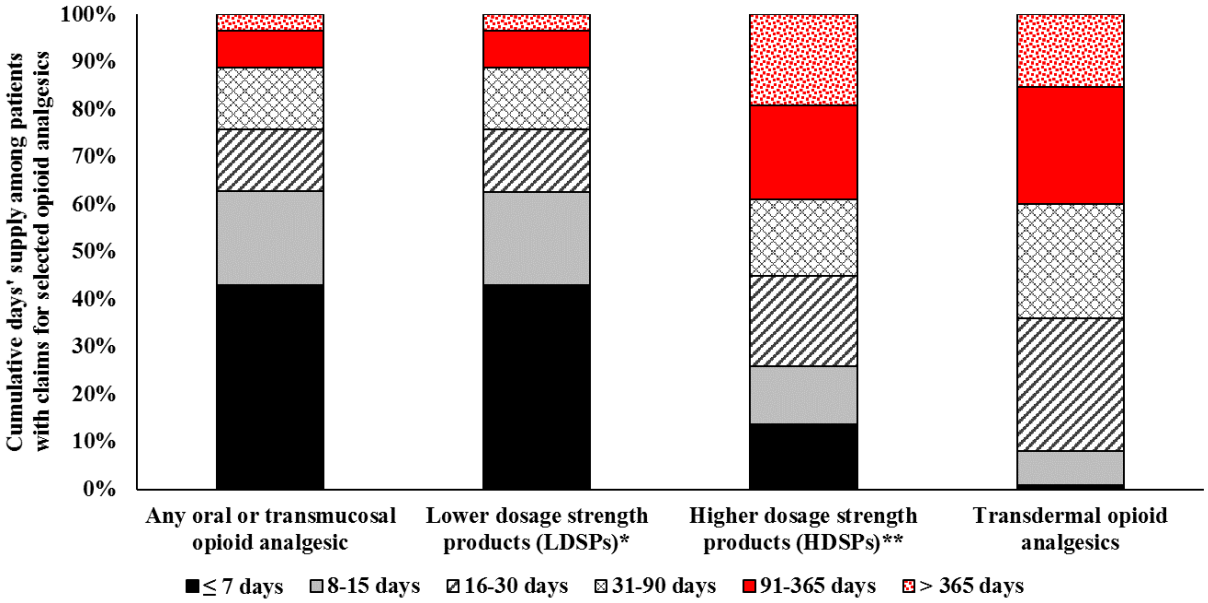
‡ Modified Charlson Comorbidity Index was evaluated using claims in the 183 days prior to a patient's first claim for the oral, transmucosal, or transdermal OA. Algorithm was derived from: Charlson ME, Pompei P, Ales KL, MacKenzie C, Ronald. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chron Dis*. 1987;40(5):373-83.

4.2.2.4 Cumulative length of therapy

We evaluated patients' cumulative length of therapy for each of the three product categories: HDSPs, LDSPs, and transdermal OAs. On average, the cumulative HDSP durations of therapy were roughly similar to those for transdermal OAs and longer than those for LDSPs. Among patients who started HDSPs, approximately 45% of patients had a cumulative HDSP length of therapy of ≤ 30 days, and 55% had a cumulative HDSP length of therapy of > 30 days (Figure 6 below). In 19% of patients who started HDSPs, the cumulative length of HDSP therapy was > 365 days. Among patients who started LDSPs, 76% of patients had a cumulative LDSP length of therapy of ≤ 30 days and 24% had a cumulative LDSP length of therapy of > 30 days. For comparison, 36% of patients who started transdermal OAs had a cumulative length of

transdermal OA therapy of ≤ 30 days and 64% had a cumulative length of transdermal OA therapy of > 30 days.

Figure 6. Cumulative days' supply of higher and lower dosage strength oral or transmucosal OAs and transdermal OAs in the Sentinel Distributed Database, January 2012 through June 2018.



Source: Sentinel Distributed Database, January 2012-June 2018. This data includes the 100% Medicare Fee-for-Service population from 2012 through 2016 and therefore age distributions in this analysis may differ from nationally representative age distributions of patients receiving OAs, with an overrepresentation of patients aged 65 years or older. Days' supply were not necessarily indicative of the actual number of days of OA therapy. Each therapy group (e.g. HDSPs, LDSPs) contains multiple OA agents, multiple dosage formulations, and varying strengths.

* Lower dosage strength products (LDSPs) were defined in this analysis as oral or transmucosal OA products which, when one unit (e.g. tablet, lozenge) is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result a total daily dose of < 90 MME.

** Higher dosage strength products (HDSPs) were defined in this analysis as oral or transmucosal OA products which, when one unit is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result a daily dose of ≥ 90 MME.

4.2.2.5 Concomitant use of selected medications

We evaluated concomitant use of selected medications based on pharmacy claims for the three product categories, HDSPs, LDSPs, and transdermal OAs. Approximately 37%, 28%, and 12% of dispensing claims for HDSPs were concomitant with dispensing claims for benzodiazepines, gabapentinoids[s], or Z-drugs[t], respectively (Table C5 in Appendix C). Concomitancy with these drugs was lower for LDSPs; approximately 24%, 20%, and 8% of dispensing claims for LDSPs were concomitant with dispensing claims for benzodiazepines, gabapentinoids, or Z-drugs,

[s] Gabapentinoids included gabapentin and pregabalin.
[t] Z-drugs included eszopiclone, zaleplon, and zolpidem.

respectively. OA claims may have been concomitant with claims for multiple medications of interest. In addition, 44% of claims for HDSPs were concomitant with claims for LDSPs. For comparison, 30%, 31%, 11%, and 60% of dispensing claims for transdermal OAs were concomitant with benzodiazepines, gabapentinoids, Z-drugs, and LDSPs, respectively.

4.2.3 Review of published studies describing the clinical and demographic characteristics of patients who received higher dose OAs

We identified two published studies that characterized patient populations receiving higher DD of OAs, describing their pain indications, comorbidities, and demographics. Both studies focused on patients with chronic, non-cancer pain (CNCP). Of note, these data were fairly old and may not accurately reflect current clinical use patterns.

- Morasco, et al. (2010)[14] examined factors associated with chronic, high dose OA therapy among 19,677 veterans who had chronic, non-cancer pain that was moderate-to-severe, and who were treated at Veterans Administration (VA) Medical Centers in the Pacific Northwest, 2008. There were three categories of exposure: no OAs, 5-179 MME/day, and ≥180 MME/day (higher DD).
- Merrill, et al. (2012)[15] reported characteristics of 1,883 adults who were recruited into their study from patients treated with chronic OA therapy for non-cancer pain while enrolled at Kaiser Permanente Northwest (KPNW), 2008-2009. Participants were categorized according to their daily dose: 1-19 MME/day, 20-49 MME/day, 50-119 MME/day, ≥120 MME/day (higher DD).

These studies found that patients who received higher DDs of OAs (≥180 MME/day in the VA study and ≥120 MME/day in the KPNW study) were likely to have multiple pain conditions (Tables 3,4). The VA study found the most common were low back pain; neck or joint pain; and rheumatism or arthritis. Also, patients who received higher DDs had a higher average pain score and were also more likely to have a history of substance abuse, compared to patients on lower DDs. The studies could not establish a clear temporal relation between the onset of substance abuse and receipt of chronic, higher dose OA therapy. The VA study also found that numerous medical and psychiatric diagnoses were more prevalent among patients who received chronic, higher DDs for CNCP, compared to patients on lower DDs, and that average chronic disease comorbidity, as measured by Charlson index, was higher (Table 3). However, the KPNW study found that the Charlson index was similar across OA dose categories (Table 4).

Table 3. Pain condition, medical, and psychiatric diagnoses in the past five years by receipt of chronic OA therapy at a high daily dose (≥180 MME), traditional daily dose (5-179 MME), or no OAs: 1,478 U.S. Veterans with chronic, non-cancer pain, 2008.

	High-dose OA (*n*=78)	Traditional-dose OA (*n*=500)	No OA (*n*=500)	*P*-value
Past-year Charlson Comorbidity Index, mean (SD)	1.2 (1.6)[a]	1.0 (1.5)[a,b]	0.9 (1.4)[b]	0.006
Pain diagnoses				
Fibromyalgia	79 (16.5%)	55 (11.0%)	31 (6.2%)	< 0.001
Inflammatory bowel disease	35 (7.3%)	22 (4.4%)	14 (2.8%)	0.004
Low back pain	399 (83.5%)	371 (74.2%)	234 (46.8%)	< 0.001
Migraine headache	102 (21.3%)	112 (22.4%)	72 (14.4%)	0.002
Neck or joint pain	392 (82.0%)	401 (80.2%)	315 (63.0%)	< 0.001
Neuropathy	86 (18.0%)	54 (10.8%)	56 (11.2%)	0.001
Rheumatism/ arthritis	343 (71.8%)	321 (64.2%)	236 (47.2%)	< 0.001
Medical diagnoses				
Hypertension	298 (62.3%)	346 (69.2%)	292 (58.4%)	0.002
Congestive heart failure	59 (12.3%)	43 (8.6%)	32 (6.4%)	0.005
Myocardial infarction	34 (7.1%)	32 (6.4%)	21 (4.2%)	0.13
Diabetes	151 (31.6%)	129 (25.8%)	133 (26.6%)	0.09
Sleep apnea	97 (20.3%)	96 (19.2%)	82 (16.4%)	0.27
Cerebrovascular disease	57 (11.9%)	51 (10.2%)	51 (10.2%)	0.61
Peripheral vascular disease	55 (11.5%)	45 (9.0%)	38 (7.6%)	0.11
Chronic pulmonary disease	176 (36.8%)	175 (35.0%)	146 (29.2%)	0.03
Paraplegia and/or Hemiplegia	26 (5.4%)	16 (3.2%)	11 (2.2%)	0.02
Psychiatric diagnoses				
Major depressive disorder	320 (66.9%)	303 (60.6%)	200 (40.0%)	< 0.001
Dysthymic disorder	87 (18.2%)	62 (12.4%)	50 (10.0%)	0.001
Bipolar disorder	28 (5.9%)	45 (9.0%)	42 (8.4%)	0.15
Panic disorder	33 (6.9%)	35 (7.0%)	15 (3.0%)	0.008
Posttraumatic stress disorder	179 (37.4%)	169 (33.8%)	134 (26.8%)	0.001
Other anxiety disorder	122 (25.5%)	122 (24.4%)	79 (15.8%)	< 0.001
Schizophrenia	13 (2.7%)	24 (4.8%)	18 (3.6%)	0.23
Any sleep disorder	103 (21.5%)	102 (20.4%)	64 (12.8%)	0.001
Any alcohol or substance use disorder	175 (36.6%)	165 (33.0%)	114 (22.8%)	< 0.001
Nicotine disorder	172 (36.0%)	157 (31.4%)	99 (19.8%)	< 0.001

Source: Morasco, et al. (2010)[14]

Table 4. Characteristics of 1,883 patients receiving chronic opioid therapy for non-cancer pain, by average daily dose, Kaiser Permanente Northwest, 2008-2009.

	Daily dose[a], MME				
	1-19	20-49	50-119	≥120	*P*-value[b]
Number of patients (weighted %)	216 (25.7%)	332 (35.5%)	724 (23.1%)	611 (15.7%)	
Female, %	65.4	59.7	64.4	59.6	.30
Mean age (S.E.), y	58.5 (0.9)	55.7 (0.8)	54.8 (0.6)	52.6 (0.5)	< .001
BMI (S.E.)	32.2 (0.7)	30.3 (0.5)	30.8 (0.7)	30.3 (0.4)	.26
Some college education, %	60.4	58.3	59.2	65.9	.43
Mean days with pain in prior 6 months (SE)	163.8 (3.2)	171.4 (2.1)	168.5 (1.7)	167.3 (1.6)	.17
Using opioids for more than one pain condition, %	62.7	64.6	59.8	73.2	.002
Predominate use of long-acting opioids in the prior 3 months, %	2.4	20.8	50.7	75.6	<.001
Self-reported drug or alcohol problem, %	15.7	22.9	21.9	30.9	.053
Mean Charlson index (S.E.)	1.3 (0.2)	1.0 (0.1)	1.2 (0.1)	1.4 (0.1)	.048
Number of times per day took opioids last 2 weeks (SE)	2.1 (0.07)	3.0 (0.09	3.3 (0.08)	3.7 (0.24)	<.001
Average pain intensity (0–10) (SE)	5.7 (0.14)	5.8 (0.14)	5.9 (0.1)	6.1 (0.09)	<.001
Mean Pain Impact Score (0–10) (SE)	6.0 (0.24)	6.9 (0.23)	7.3 (0.16)	7.9 (0.15)	<.001
Rate opioids as very or extremely helpful, %	57.2	53.2	61.2	66.0	.26

SE, standard error

Source: Merrill, et al. (2012)[15]

[a] Average daily dose in the past three months

[b] *P*- values were adjusted for health plan, gender, age and opioid type (predominant use of long- versus short-acting opioids), except for the *P*-values for gender (controlled for age and type), age (controlled for gender and type) and predominant use of long-acting opioids (controlled for gender and age).

4.3. Review of the epidemiologic literature on the associations between higher dose OAs and the risks of abuse, addiction, and overdose

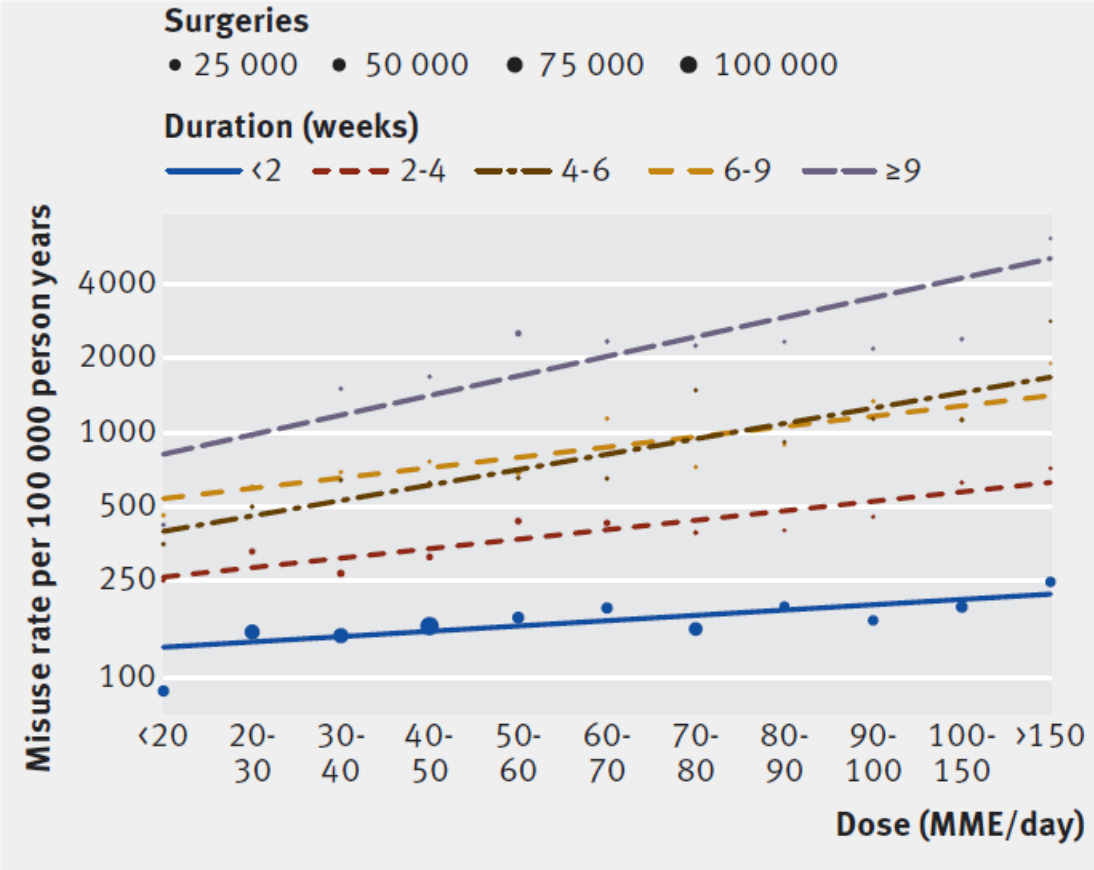
4.3.1 Association between prescribed OA DD and risks of abuse or addiction

Few epidemiologic studies have examined the association between prescribed OA daily dose and risk of abuse or addiction, and we identified no studies examining these risks in relation to opioid

product dosage strength received (**Appendix E summarizes the studies' design features and results**). Because many patients hide their opioid abuse and often have difficulty accessing treatment or getting insurance coverage for treatment of substance use disorders, healthcare data imperfectly capture opioid abuse and addiction, and therefore it can be challenging to determine the onset of opioid abuse or addiction using these data. Outcomes are incompletely captured, and it is difficult to establish that an OA prescription precedes the onset of opioid abuse using healthcare data alone. Section 5.3.1 discusses other design limitations, including the challenge of measuring daily dose accurately using healthcare claims data. Acknowledging these limitations, we identified three studies with designs and analyses that allowed for cautious interpretation of the results.

In one study[16] of post-surgical patients with minimal recent pre-operative exposure to prescription OAs, DD was very weakly but significantly associated with opioid misuse (a composite outcome defined here as ICD-9 claim for opioid dependence, abuse, or overdose/poisoning, comprising codes for prescription opioids only), after adjusting for duration of OA therapy, active pharmaceutical ingredient (API) of opioid product, benzodiazepine prescription dispensing, patient sex, age, surgery year, state, surgery type, and comorbidity diagnosis codes (psychiatric, non-cancer pain, morbid obesity). Importantly, the claims-based outcome definition was not validated with medical records and claims data have been shown to under-ascertain opioid use disorder and abuse,[39] as discussed further in Section 5.3.1. Duration of use was more strongly associated than was DD with opioid misuse, and duration also appeared to modify the association between dose and misuse, as illustrated in Figure 7, which displays a plot of the association of daily dose and unadjusted rate of misuse within strata of duration (Figure 7).[16] Visually, there was a small difference in risk between higher and lower doses when total duration was short, and there was a larger risk differential when total duration was long.[16]

Figure 7. Rates of misuse* by DD and duration of postsurgical OA prescription: 1,015,116 U.S. adults, 2008-2016.



*Unadjusted rate of misuse, defined as ICD-9 code for opioid use disorder, dependence, or overdose.
Surgeries refers to the number of surgeries at that daily dose. The size of the dots represents the number of surgeries.
Source: Brat, et al. (2018) Figure 3(E)[16]

Two other administrative claims-based studies[17,18] used DD, plus other variables, to predict the risk of subsequent opioid abuse among patients with non-cancer pain, either chronic or acute. The anticipated application of these models was to predict a patient's future risk of abusing OAs, using their OA utilization patterns and other factors to guide clinical decision-making about OA prescribing and other medical treatment. In one study,[17] among prevalent OA users, daily dose ≥120 MME was associated with a doubling in the incidence of opioid abuse (defined here as an ICD-9 claim for opioid abuse or dependence), after adjusting for acute vs. chronic opioid use (≥90 days' supply) and medical and demographic factors. The study also found that OA users with ≥90 days' supply had more than four times the incidence of opioid abuse as patients with 1-89 days' supply.[17]

In the second study,[18] among incident users of chronic OA therapy (i.e., patients who received ≥90 days' supply after at least 12 months with no OA prescriptions), an automated, data-driven method selected threshold values of three variables – higher daily dose, longer duration of opioid

therapy, and younger age – to classify patients as being at a higher risk of opioid abuse (defined here as ICD-9 codes for opioid abuse, dependence, or overdose). However, the model was not accurate enough in predicting a patient's future risk of opioid abuse to inform clinical decision-making.

4.3.2 Association between prescribed OA DD and risk of overdose

We identified and reviewed 21 studies[8,19-38] examining the association between OA DD and the risk of overdose among patients prescribed OAs; most excluded patients with cancer or terminal illness. No study examined the relationship between OA product dosage strength and risk of overdose. **Appendix F summarizes the design and results of all reviewed studies.**

These studies consistently demonstrated that, relative to lower doses, higher OA DDs were associated with a higher risk of opioid overdose.[19,22,38] A major distinction among the studies we reviewed was the definition of overdose: some studies defined the outcome as fatal opioid overdose only,[20,22-24] determined from death records, whereas others defined the outcome as non-fatal or fatal opioid overdose, as determined from administrative databases of healthcare claims alone.[26,27,30,37]

Studies of fatal opioid overdose consistently found increasing risk of overdose death with each increasing category of dose (e.g., 10-MME/day increments;[8] or categories[20,31] of 1-19 [reference], 20-49, 50-99, ≥100). A matched case-control study[38] nested in the VA modeled daily dose as a continuous variable, with the aim of identifying a dosage threshold for determining clinical risk of prescription opioid overdose (unintentional or undetermined intent), accounting for patient comorbidities such as history of SUD. The study found no dosage threshold that was useful for determining clinical risk.[38] Of note, although the average daily dose was substantially higher among the cases than among the controls (median MME/day: 60 vs. 25), 67% of cases had a daily dose ≤90 MME/day on record when they died, and 41% of cases had a daily dose ≤50 MME.[38]

Increasing category of daily dose was also associated with increasing risk of non-fatal or fatal opioid overdose, as determined by administrative claims data alone, but the associations were generally weaker than the results of studies of fatal opioid overdose.[32,37] Some studies found that overdose risk was similar in patients prescribed 20-49 MME/day, relative to the reference of 1-19 MME/day, after adjusting for patient comorbidities, concomitant prescriptions for sedative medications, and other confounders.[19,32,37]

Most studies included both intentional and unintentional opioid overdoses.[8,19-21,29,30,32-34,37] Among VA patients with a chronic pain diagnosis in 2004-2005, the risk of intentional, fatal overdose increased in higher categories of prescribed daily dose, after adjusting for diagnoses of pain, mental illnesses, and other medical conditions.[31] The associations were of similar magnitude when the outcome was completed suicide, either by overdose or other means.[31]

Notably, while these studies aimed to examine the association between prescribed OA dose and risk of overdose, a substantial minority of prescription opioid overdose decedents had no OA prescription on record during the study period. For example, 25% of prescription opioid overdose decedents in North Carolina had no prescription OA in the state PDMP during that year,[8] and 40% of prescription opioid overdose decedents who were VA patients in 2004-2005 had no prescription OA recorded in their VA record in the 1-4 years before their death.[22]

Finally, in addition to OA daily dose, other risk factors exhibited strong, independent associations with opioid overdose risk among patients prescribed OAs. In studies that reported these associations, prescriptions for benzodiazepines[28,33] and skeletal muscle relaxants,[33] and diagnosis of depression[26] were associated with a greater increase in the risk of overdose than the increase associated with an OA daily dose ≥100 MME/day relative to 1-19 MME/day, after adjusting for other patient medical and healthcare utilization factors and demographics.

5. SUMMARY AND INTERPRETATION OF FINDINGS

5.1. U.S. prescribing and clinical use of HDSPs and higher DD OAs

5.1.1 National prescribing patterns and trends

Out of all oral or transmucosal OAs dispensed in the U.S. in the last 6 years, products with higher MME content per unit (e.g. tablet, lozenge) represented a very small proportion. Of patients dispensed at least one oral or transmucosal OA prescription in 2018, less than 1% of patients received products with ≥ 90 MME per unit. Products with < 20 MME per unit comprised 87% or more of all prescriptions for oral or transmucosal OAs dispensed in 2018, and products with ≥ 90 MME per unit comprised less than 1% of prescriptions. From 2013 to 2018, HDSP prescriptions decreased 63%, compared to 31% and 34% decreases in prescriptions for LDSPs and transdermal OAs, respectively. Results of the analyses in the Sentinel data revealed a similarly low proportion of OA pharmacy claims consisting of HDSPs, when defined as products which, if one unit (e.g. tablet, lozenge) were taken at the lowest labeled frequency, would result in a daily dosage of ≥ 90 MME per day.

The estimated volume of higher DD OA prescriptions dispensed in the US fell substantially from 2006 to 2017, both when expressed as a prescription rate per population and as a percentage of all OA prescriptions. Substantial inter-state variability was evident in the rate of higher daily dose OA prescriptions per population, and this variability also diminished from 2006 to 2017.

5.1.2 Clinical use of higher dose OAs

Selected health systems responded to FDA's scientific inquiry about the clinical needs for higher dosage strength OA products. They identified clinical needs as treating pain in patients with:

- Cancer
- Terminal illness in need of palliative or hospice care
- More rarely, complex chronic conditions, e.g., sickle cell disease, often with high comorbidity

The higher dosage strength products were reported as being useful for:

- Reducing pill burden, a practical factor that is important for patients with cancer or at end-of-life
- Dispensing high daily doses of OAs given the limits some payers make on the number of pills they will cover per prescription or per month

All responding health systems also indicated that states, payers, or both had placed limits on the amount of OAs prescribed. The indications identified as the primary clinical needs for HDSPs, i.e., treating pain in patients with cancer or at end-of-life, were excepted from these restrictions. Prescribers could also seek exceptions through prior authorization procedures for patients with severe, chronic pain related to other conditions. There were no data on the impact on patient outcomes from these restrictions. Many patients and providers acknowledged the need for restrictions on OA prescribing, but there were concerns about delayed or reduced access to effective pain management and resultant harm to patients.

The Sentinel claims-based analysis found that, compared to patients starting LDSPs, patients starting HDSPs tended to be medically complex patients with multiple pain-related diagnoses, higher comorbidity scores, and a higher prevalence of claims with diagnoses related to mental health conditions or substance use disorders. Among patients starting HDSPs or transdermal OAs, the most commonly seen diagnostic code categories were related to arthritis and nontraumatic joint conditions, back pain or other back conditions, and nervous system conditions. Approximately 30% of patients starting an HDSP had a diagnosis claim for cancer. The Sentinel analyses also showed a longer duration of use for HDSPs, compared to LDSPs.

Similarly, published studies found that patients on higher DD OAs were likely to have multiple pain conditions, most commonly low back pain; neck or joint pain; and rheumatism or arthritis. On average, they had a higher average pain score and were also more likely to have a history of substance abuse, compared to patients on lower DDs. Importantly, the studies could not establish a clear temporal relation between the onset of substance abuse and receipt of chronic, higher dose OA therapy.

5.2. Data and methods considerations

In this review, HDSPs and higher DD OAs were defined in a variety of ways in both FDA analyses and in the studies we reviewed. Our goal was to provide multiple views of higher dose OA prescribing and clinical use, while also to account for differing formulations and dosing intervals. By nature, OA dosing is a continuous variable along a spectrum or range of dosing, without a natural cut-point or threshold defining high versus low dosage strength or daily dose. Therefore, our dichotomization of higher versus lower dosage strength products was essentially arbitrary although based in part upon published OA prescribing guidelines.[9] Finally, any classification of OA dose that includes multiple opioid moieties involves MME calculations, which are an evolving field of research and not well standardized.

Results presenting nationally estimated counts of prescriptions and patients were based on projections of sample prescription claims data and therefore have some degree of inherent sampling error. These estimates are not intended to be representations of exact enumerations and should be interpreted with some caution. Furthermore, the prescription and patient counts were derived from prescriptions dispensed from outpatient retail pharmacies. Prescription activity from non-retail pharmacies, such as mail-order, long-term care, and hospital pharmacies, were not included in the results. Additionally, indication for use is not directly linked to dispensed prescription data. Therefore, the indication for OA therapy is not available in the national estimates of prescription counts and patient counts.

The analyses of oral, transmucosal, and transdermal OA use patterns using administrative claims data are estimates which included a large number of Medicare beneficiaries. Patients aged 65 years or older were overrepresented in the patient sample, and accordingly age-related results should be interpreted with caution. A patient's healthcare plan enrollment may have changed from one included healthcare insurer to another during the study time period—such as a patient turning 65 years old who becomes eligible for Medicare—which would cause the patient to appear twice in the analysis. This phenomenon may overestimate use results but underestimate duration of use.

Furthermore, these analyses rely on reimbursed claims from commercial or government healthcare data sources. Therefore, prescriptions for OAs or medical care paid for without insurance (e.g. cash payments) or with other types of insurance not included in the distributed database would not have been included in these analyses. The results of the OA dose, duration of therapy and concomitancy analyses were derived from pharmacy claims data and do not necessarily represent the patients' actual use or dose of the medications. Possible indications for OA use were estimated in the administrative claims data using diagnosis and procedure codes on medical claims that occurred proximal to the start of oral, transmucosal, or transdermal OA therapy. Furthermore, these analyses required only a single claim with a diagnosis of interest for inclusion in a given category for pain-related condition and could have included some claims for ruling out a diagnosis. The diagnostic claims categories were not validated for this study using medical records. Therefore, our analysis may over- or underestimate the prevalence of actual medical conditions and diseases.

5.3. Review of the epidemiologic literature on the associations between higher dose OAs and the risks of abuse, addiction, and overdose

5.3.1 Association between prescribed OA DD and risks of abuse or addiction

We identified three epidemiologic studies[16-18] that measured exposure (OA dose) before the outcomes of abuse and addiction, as measured by healthcare claims related to these outcomes. These studies suggested that higher prescribed DD was weakly associated with higher risks of abuse and addiction. However, reverse causation, and more rigorous screening in people with higher DDs, may have contributed to the observed associations. The explanation for reverse causation is that patients may have entered the study with undiagnosed opioid abuse or addiction, and these conditions contributed to their escalating dose. This reverse causation is possible even when investigators restrict their sample to patients with no history of the diagnoses under study and no history of OA prescription because healthcare claims data incompletely capture opioid abuse and addiction[39] and other substance use disorders. People who abuse opioids may obtain them outside of the medical system, and stigma may lead them to hide their substance abuse from their providers. Furthermore, treatment for substance use disorders may be poorly reimbursed and therefore incompletely captured in insurance claims data, which have indeed been shown to have limited accuracy in identifying opioid use disorder.[39] Thus, it is difficult to establish that an OA prescription precedes the onset of opioid abuse by investigating healthcare data alone. Also, ascertainment of the outcome will also be incomplete in healthcare data,[39] and this may result in better capture of the outcome among patients who receive higher DDs, perhaps through more rigorous screening. This could inflate the positive association between daily dose and risks of abuse and addiction. The advantage to using healthcare claims data to study opioid abuse and addiction is the efficiency it affords for studying a large population. However, these

data have serious limitations with respect to ascertainment of these outcomes. Although these studies attempted to adjust for potential confounding by duration of OA use, the temporal relationships between dose, duration, and risk of abuse and addiction, are clearly complex[40] and may be difficult to characterize well in analyses using healthcare claims data. Furthermore, in the study by Brat et al.,[16] duration of OA therapy appeared to modify the association between higher dose and higher risk of abuse or addiction. The increase in risk associated with increase in dose appeared to be stronger among patients who received ≥9 weeks' supply of OA therapy, compared with patients who received <2 weeks' supply.[16]

Categorizing patients by OA exposure level (OA DD) is a challenge in studying the association between opioid daily dose and the risks of abuse and addiction. Some variation is expected between pharmacy-ascribed daily dose and actual patient consumption. Both over- and under-estimation of DD are possible but have not been quantified, to our knowledge; so, their expected impact on the results is unpredictable.

The investigators adjusted for medical and psychiatric disorders that may confound the association between OA and the risks of abuse and addiction[41] by finding documentation of insurance reimbursement for treating these disorders and entering them in a regression model. Still, these data on these confounders may be incomplete, e.g., if patients receive care outside the health plan or have an undiagnosed disorder. This can result in residual confounding, biasing the associations between dose and risks of abuse and addiction—potentially resulting in spurious or exaggerated associations that do not reflect a true causal relationship.

Finally, the limited evidence on the association between OA daily dose and risks of abuse and addiction comes mainly from U.S. adults insured by private, commercial insurance,[16-18] with some inclusion of adults covered by Medicare.[18] These findings may not generalize to adults covered by public insurance, or to adolescents.

The association between OA DD and risks of abuse and addiction observed in claims-based studies requires further study using prospective data collection and validated instruments for measuring abuse and addiction in populations receiving opioids for pain. To this end, manufacturers of ER/LA OAs are currently conducting these prospective studies, with FDA oversight, to fulfill FDA postmarketing requirements.[42] Complementary data from other research disciplines such as ethnography and clinical neuroscience may also have value for understanding the relationship between dose and risk of abuse and addiction.

5.3.2 Association between prescribed OA DD and risk of overdose

Epidemiologic studies of patients prescribed OAs for non-cancer pain have consistently found that higher DD is associated with higher risks of intentional and unintentional opioid overdose, after adjusting for medical and psychiatric conditions and concomitant medications.[19,22,25,32,33,37,38] Because the literature includes several rigorous studies[22,38] with robust ascertainment of exposure and outcome and adjustment for confounding, the preponderance of evidence suggests that DD likely does contribute causally to the observed increased risk in overdose. The positive association appears to be linear,[8,22,38] and a threshold for prescribed OA dose that discriminates well between low and high risk has not been found.[8,38] It is important to note, however, that a substantial proportion of opioid overdoses occur among

patients with prescriptions for lower DD of OA,[38] and multiple factors other than DD are also important in identifying patients at elevated risk of overdose. These include, but are not necessarily limited to, age,[20] history of substance use disorder,[34] depression,[26] and prescriptions for benzodiazepines[28] or muscle relaxants.[33]

Many of the limitations of studies examining the association between OA dose and abuse or addiction also apply to studies looking at the outcome of overdose. This section explains several additional methodological considerations that influenced our interpretation of the study results. Where applicable, it refers to relevant methodological considerations from the preceding section on discussion of the association between OA daily dose and risks of abuse and addiction.

5.3.2.1 Defining DD and categorizing patients by exposure level

Some variation is expected between pharmacy-ascribed dose in electronic healthcare data and actual patient consumption, as discussed above. The studies that examined all subsequent overdose deaths among patients prescribed OAs in a given period found a substantial proportion of decedents had no current prescription on record when they died.[8,22] Other studies required patients to have a current prescription on record to count as having the event of interest, but they may also have obtained opioids or other medications from sources other than their own prescription.[43]

Opioid overdose is an acute event, and the prescribed OA dosage can change every time a prescription's supply runs out. Thus, it seems advantageous to model daily dosage as a time-varying exposure,[22,26,27] or even to design the study so that only patients with a current prescription would count as having the event of interest.[38] However, these studies are limited in that they do not measure the actual consumption behavior or events occurring after the end of the calculated days' supply of prescribed OA. A causal pathway from prescription to overdose may take months or more, with development of abuse and addiction as potential intermediaries. Another variable in the complex interaction of factors that lead to overdose is a patient's OA dose trajectory and variability, which may affect a patient's opioid tolerance. A new study examined the association between OA dose variability and risk of opioid overdose among patients treated with OAs for ≥90 days for CNCP and found that higher variability in a patient's OA dose was associated with a greater risk of opioid overdose, after adjusting for average recent OA daily dose and other patient medical and demographic factors.[44] The study authors acknowledged the behavioral and biological mechanisms that may have contributed to the positive association. Therefore, measuring the association of prescribed dosage with patient overdose in the short-term may miss important pathways in the risks attributable to OA use. Furthermore, the studies were not designed to examine the safety risks to the other members of the household associated with prescribed OA DD.

5.3.2.2 Defining the outcome of opioid overdose

The studies in this review also varied in their definition of the overdose outcome. An example of rigorous outcome definition was from the study by Bohnert, et al. (2016)[38]: fatal opioid overdose that was unintentional or undetermined intent, as measured in cause-of-death records from the National Death Index. Other studies defined the outcome as fatal opioid overdose, regardless of

intent.[8,19-21,29,30,32-34,37] Notably, OA DD exhibited a linear association with risk of intentional opioid overdose.[31]

There are several important limitations to studying overdose using claims data alone.[26,27,29,30,32] First, these studies would not capture fatal overdoses that did not generate a medical claim. This may have introduced bias if people using higher doses of OAs were more likely to have an overdose that was rapidly fatal. Second, the accuracy of outcome classification was uncertain, because the claims-based overdose algorithms were not validated against medical records within the data environment in which the studies were conducted. While ICD-9 codes for any opioid overdose performed well in a study conducted within the Kaiser Permanente Northern California health plan, 2003-13,[45] some variation would be expected when a claims-based algorithm definition of overdose is applied to other populations, based on changes in care depending on period, health plan, and geographic region.

5.3.2.3 Adjusting for confounders and assessing interaction

Most of the studies we reviewed used available data on healthcare claims for concomitant medications and medical and psychiatric diagnoses to adjust for potential confounders. Still, this adjustment does not eliminate confounding by undiagnosed or unrecorded medical and psychiatric conditions, as discussed in the previous section. Strong, positive associations between OA DD and overdose risk were found after adjusting for depression and other psychiatric disorders,[33,38] which are important confounders as these conditions have strong associations with both OA dose and risk of overdose.[26,28,34] Several studies stratified the analysis of DD and overdose risk by the presence of depression,[26] or by psychiatric medications such as benzodiazepines,[28,33] to assess for a potential interaction. The positive, linear association between DD and opioid overdose risk did not appear to depend on the presence of depression diagnosis[26,28] or benzodiazepine prescription.[28]

5.3.2.4 Applying the results to other populations

Apart from a study's validity in measuring the association, the applicability of the association to other populations, i.e., generalizability, depends on several factors. The evidence on the association between OA DD and overdose risk has some strengths and weaknesses pertaining to its generalizability. A strength was that evidence for a positive association derives from diverse populations, including U.S. veterans;[25,38] as well as U.S. adults insured by private, commercial insurance[19,26,27] and state Medicaid.[30,32,33] One limitation was that many of these studies used data that predated the secular decline in prescriptions for all OAs, including high dose prescriptions. Another limitation was that patients had to be enrolled in the health plan for a sufficient length of time (e.g., two years) to be included in the study, so that there were records for measuring the outcome as well as measuring covariates before study baseline. This inclusion criterion may have restricted the study population to people with poorer baseline health status (as people in worse health may be more likely to remain on their health plan) or better baseline health status (as people had to survive 12 months post-prescription), but the studies did not compare baseline health status of people excluded from to those included in the study sample.

6. CONCLUSIONS

Higher dosage strength oral and transmucosal OA products comprised a very small proportion of overall OA utilization in the U.S., and prescription numbers for these products decreased at a faster rate than for lower dosage strength and transdermal OA products between 2013 and 2018.

Several large healthcare consortiums reported that the primary clinical needs for HDSPs were to treat patients with cancer, palliative care, or end-of-life care, and that a rare clinical need was to treat patients with severe pain from other complex conditions. However, an analysis of a distributed database of administrative healthcare claims nationwide network of claims found that fewer than one-third of patients who started HDSPs had a proximal claim with a diagnosis related to cancer. Among patients starting HDSPs the most commonly seen diagnostic code categories were related to arthritis and nontraumatic joint conditions, back pain, or nervous system conditions. Medical and psychiatric comorbidity was higher among patients prescribed HDSPs relative to patients prescribed LDSPs. Patients who started HDSPs appeared to be clinically similar to patients who started therapy with transdermal OA products.

The published epidemiologic literature on risks associated with higher dose OAs focused on total average daily dose, and none of the studies reviewed compared the risks of abuse, addiction, and overdose among patients prescribed HDSPs, relative to patients prescribed LDSPs. Limited epidemiologic evidence from published healthcare claims-based studies suggests an association between higher prescribed DD and increased risks of abuse and addiction. However, due to the limitations of healthcare data, including the difficulty establishing temporal relationships, it remains unclear whether the higher dose plays a causal role in the development of opioid addiction. To more fully understand this relationship, additional evidence is needed from prospective epidemiologic studies and other research disciplines.

The epidemiologic evidence suggests that higher DD of OAs likely contributes causally to increased risk of intentional and unintentional opioid overdose, although DD is only one of multiple, important factors influencing overdose risk. The association between DD and overdose risk appears to be linear, with no threshold value for prescribed DD that discriminates well between patients who will versus will not go on to have an overdose, and a substantial proportion of prescription opioid overdoses occur among patients prescribed lower DDs or with no OA prescription on record at all.

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8. APPENDICES

8.1. Appendix A. Glossary of selected terms used in this review

For the purposes of this review, we used the following definitions:

DD – Daily dose, defined in the literature reviewed for this document as the calculated value of Morphine Milligram Equivalents (MME) per day available from a given prescription, from the prescription record, assuming the patient consumed the same quantity of product every day over the recorded days' supply.

HDSP – Higher Dosage Strength Product, defined in FDA analyses as an oral or transmucosal opioid analgesic product, by opioid moiety, dosage strength, and formulation, at the higher end of the range of marketed opioid analgesic products in terms of MMEs. Specific definitions used in FDA analyses are described in Sections 3.3.1 and 3.3.2.

LDSP – Lower Dosage Strength Product, defined in FDA analyses as an oral or transmucosal opioid analgesic product, by opioid moiety, dosage strength, and formulation, not at the higher end of the range of marketed opioid analgesic products in terms of MMEs. Specific definitions used in FDA analyses are described in Sections 3.3.1 and 3.3.2.

MME – Morphine Milligram Equivalents, defined as the milligram strength of a specified quantity of an opioid analgesic product when expressed as equivalent to oral morphine. See further discussion of MME and data sources used to calculate MME in FDA's analyses in Section 3.1.

OA – Opioid Analgesic, referring broadly to any approved opioid agonist medication indicated for the management of pain, and excluding products indicated specifically for the treatment of opioid use disorder.

Potency – An expression of the functional activity of a drug, in terms of the concentration or amount needed to produce a defined effect.[46] Potency depends on a number of factors such as both receptor (affinity, efficacy) and tissue (receptor numbers, drug accessibility) parameters, although low affinity compounds do not tend to be of high potency.[47]

8.2. Appendix B. Drug utilization database descriptions/limitations

Sentinel Distributed Database
The Sentinel Distributed Database (Sentinel) comprises data on approximately 292.5 million members from 18 Data Partners from 2000 to 2017, including 66.9 million members who are currently enrolled and contributing data. All Data Partners contribute administrative, medical, and pharmacy insurance claims and demographic data. The majority of individuals in the distributed database is privately insured, with approximately half of individuals between ages 18 and 65 years.

IQVIA National Prescription Audit™
The IQVIA National Prescription Audit (NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 58,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

IQVIA Total Patient Tracker™ (TPT)
IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of ~58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies.

8.3. Appendix C. Data tables and figures

Table C1. Opioid analgesic products included in the Sentinel Distributed Database analyses.

Lower dosage strength oral or transmucosal opioid analgesic products*

Non-proprietary name	Dosage form/route	Strength
acetaminophen with codeine	solution/elixir/suspension	120-12 mg/5 mL
acetaminophen with codeine	tablet	300-15 mg
acetaminophen with codeine	tablet	300-30 mg
acetaminophen with codeine	tablet	300-60 mg
acetaminophen with codeine	tablet	30-650 mg
acetaminophen with codeine	tablet	60-650 mg
acetaminophen/caffeine/dihydrocodeine	capsule	320 5-30-16 mg
acetaminophen/caffeine/dihydrocodeine	capsule	356 4-30-16 mg
acetaminophen/caffeine/dihydrocodeine	tablet	325-30-16 mg
acetaminophen/caffeine/dihydrocodeine	tablet	712 8-60-32 mg
aspirin/caffeine/dihydrocodeine	capsule	356 4-30-16 mg
buprenorphine	film	150 mcg
buprenorphine	film	75 mcg
butorphanol	nasal spray	25mg
butalbital/acetaminophen/caffeine/codeine	capsule	50-300-40-30 mg
butalbital/acetaminophen/caffeine/codeine	capsule	50-325-40-30 mg
butorphanol tartrate	spray, non-aerosol	10 mg/mL
carisoprodol/aspirin/codeine	tablet	200-325-16 mg
codeine/butalbital/aspirin/caffeine	capsule	30-50-325-40 mg
codeine	solution	30 mg/5 mL
codeine	tablet	15 mg
codeine	tablet	30 mg
codeine	tablet	60 mg
fentanyl	spray, non-aerosol	100 mcg/spray
fentanyl	spray, non-aerosol	200 mcg/spray
fentanyl	tablet, effervescent	100 mcg
fentanyl	tablet, sublingual	100 mcg
hydrocodone	capsule, oral only, ER 12hr	10 mg
hydrocodone	capsule, oral only, ER 12hr	15 mg
hydrocodone	capsule, oral only, ER 12hr	20 mg
hydrocodone	capsule, oral only, ER 12hr	30 mg
hydrocodone	capsule, oral only, ER 12hr	40 mg
hydrocodone	capsule, extended release 12 hr	10 mg
hydrocodone	capsule, extended release 12 hr	15 mg
hydrocodone	capsule, extended release 12 hr	20 mg
hydrocodone	capsule, extended release 12 hr	30 mg
hydrocodone	capsule, extended release 12 hr	40 mg
hydrocodone	tablet, oral only, ext rel 24 hr	20 mg
hydrocodone	tablet, oral only, ext rel 24 hr	30 mg
hydrocodone	tablet, oral only, ext rel 24 hr	40 mg
hydrocodone	tablet, oral only, ext rel 24 hr	60 mg
hydrocodone	tablet, oral only, ext rel 24 hr	80 mg
hydrocodone/acetaminophen	capsule	5-500 mg
hydrocodone/acetaminophen	solution	10-300 mg/15 mL
hydrocodone/acetaminophen	solution	10-325 mg/15 mL
hydrocodone/acetaminophen	solution	10-325 mg/15 mL
hydrocodone/acetaminophen	solution	5-163 mg/7 5 mL
hydrocodone/acetaminophen	solution	7 5-325 mg/15 mL
hydrocodone/acetaminophen	solution	7 5-500 mg/15 mL
hydrocodone/acetaminophen	tablet	10-300 mg
hydrocodone/acetaminophen	tablet	10-325 mg
hydrocodone/acetaminophen	tablet	10-400 mg
hydrocodone/acetaminophen	tablet	10-500 mg
hydrocodone/acetaminophen	tablet	10-650 mg
hydrocodone/acetaminophen	tablet	10-660 mg
hydrocodone/acetaminophen	tablet	10-750 mg
hydrocodone/acetaminophen	tablet	2 5-325 mg
hydrocodone/acetaminophen	tablet	2 5-500 mg
hydrocodone/acetaminophen	tablet	5-300 mg
hydrocodone/acetaminophen	tablet	5-325 mg
hydrocodone/acetaminophen	tablet	5-400 mg
hydrocodone/acetaminophen	tablet	5-500 mg
hydrocodone/acetaminophen	tablet	7 5-300 mg
hydrocodone/acetaminophen	tablet	7 5-325 mg
hydrocodone/acetaminophen	tablet	7 5-400 mg
hydrocodone/acetaminophen	tablet	7 5-500 mg
hydrocodone/acetaminophen	tablet	7 5-650 mg
hydrocodone/acetaminophen	tablet	7 5-750 mg
hydrocodone/acetaminophen/dietary suppl #11	combo pack	10-325 mg
hydrocodone/acetaminophen/dietary suppl #11	combo pack	10-650 mg
hydrocodone/acetaminophen/dietary suppl #11	combo pack	5-500 mg
hydrocodone/ibuprofen	tablet	10-200 mg
hydrocodone/ibuprofen	tablet	2 5-200 mg
hydrocodone/ibuprofen	tablet	5-200 mg
hydrocodone/ibuprofen	tablet	7 5-200 mg
hydromorphone	liquid	1 mg/mL
hydromorphone	tablet	2 mg
hydromorphone	tablet	4 mg
hydromorphone	tablet extended release 24 hr	12 mg
hydromorphone	tablet extended release 24 hr	16 mg

Non-proprietary name	Dosage form/route	Strength
hydromorphone	tablet extended release 24 hr	8 mg
ibuprofen/oxycodone	tablet	400-5 mg
levorphanol	tablet	2 mg
meperidine	solution	50 mg/5 mL
meperidine	tablet	100 mg
meperidine	tablet	50 mg
methadone	tablet	10 mg
methadone	tablet	5 mg
morphine	capsule, ER multiphase 24 hr	30 mg
morphine	capsule, ER multiphase 24 hr	45 mg
morphine	capsule, ER multiphase 24 hr	60 mg
morphine	capsule, ER multiphase 24 hr	75 mg
morphine	capsule, extend release pellets	10 mg
morphine	capsule, extend release pellets	20 mg
morphine	capsule, extend release pellets	30 mg
morphine	capsule, extend release pellets	40 mg
morphine	capsule, extend release pellets	50 mg
morphine	capsule, extend release pellets	60 mg
morphine	capsule, extend release pellets	70 mg
morphine	capsule, extend release pellets	80 mg
morphine	solution	10 mg/5 mL
morphine	tablet extended release	15 mg
morphine	tablet extended release	30 mg
morphine	tablet, oral only, ext rel 12 hr	15 mg
morphine	tablet, oral only, ext rel 12 hr	30 mg
morphine	tablet, oral only, extnd release	15 mg
morphine	tablet, oral only, extnd release	30 mg
morphine/naltrexone	capsule, extend release pellets	20-0 8 mg
morphine/naltrexone	capsule, extend release pellets	30-1 2 mg
morphine/naltrexone	capsule, extend release pellets	50-2 mg
morphine/naltrexone	capsule, extend release pellets	60-2 4 mg
morphine/naltrexone	capsule, extend release pellets	80-3 2 mg
morphine/naltrexone	capsule, oral only, ext rel pell	20-0 8 mg
morphine/naltrexone	capsule, oral only, ext rel pell	30-1 2 mg
morphine/naltrexone	capsule, oral only, ext rel pell	50-2 mg
morphine/naltrexone	capsule, oral only, ext rel pell	60-2 4 mg
morphine/naltrexone	capsule, oral only, ext rel pell	80-3 2 mg
oxycodone	capsule	5 mg
oxycodone	solution	5 mg/5 mL
oxycodone	tablet	10 mg
oxycodone	tablet	5 mg
oxycodone	tablet extended release 12 hr	10 mg
oxycodone	tablet extended release 12 hr	20 mg
oxycodone	tablet, oral only	5 mg
oxycodone	tablet, oral only	7 5 mg
oxycodone	tablet, oral only, ext rel 12 hr	10 mg
oxycodone	tablet, oral only, ext rel 12 hr	15 mg
oxycodone	tablet, oral only, ext rel 12 hr	20 mg
oxycodone/acetaminophen	capsule	5-500 mg
oxycodone/acetaminophen	solution	5-325 mg/5 mL
oxycodone/acetaminophen	tab, oral only, IR - ER, biphase	7 5-325 mg
oxycodone/acetaminophen	tablet	10-300 mg
oxycodone/acetaminophen	tablet	10-325 mg
oxycodone/acetaminophen	tablet	10-400 mg
oxycodone/acetaminophen	tablet	10-500 mg
oxycodone/acetaminophen	tablet	10-650 mg
oxycodone/acetaminophen	tablet	2 5-300 mg
oxycodone/acetaminophen	tablet	2 5-325 mg
oxycodone/acetaminophen	tablet	5-300 mg
oxycodone/acetaminophen	tablet	5-325 mg
oxycodone/acetaminophen	tablet	5-400 mg
oxycodone/acetaminophen	tablet	5-500 mg
oxycodone/acetaminophen	tablet	7 5-300 mg
oxycodone/acetaminophen	tablet	7 5-325 mg
oxycodone/acetaminophen	tablet	7 5-400 mg
oxycodone/acetaminophen	tablet	7 5-500 mg
oxycodone/aspirin	tablet	4 8355-325 mg
oxycodone/oxycodone terephthalate/aspirin	tablet	4 5-0 38-325 mg
oxycodone myristate	capsule, sprinkle, ER 12hr tmprr	13 5 mg
oxycodone myristate	capsule, sprinkle, ER 12hr tmprr	18 mg
oxycodone myristate	capsule, sprinkle, ER 12hr tmprr	9 mg
oxymorphone	tablet	5 mg
oxymorphone	tablet extended release 12 hr	10 mg
oxymorphone	tablet extended release 12 hr	5 mg
oxymorphone	tablet extended release 12 hr	7 5 mg
oxymorphone	tablet, oral only, ext rel 12 hr	10 mg
oxymorphone	tablet, oral only, ext rel 12 hr	5 mg
oxymorphone	tablet, oral only, ext rel 12 hr	7 5 mg
tapentadol	tablet	50 mg
tapentadol	tablet extended release 12 hr	100 mg
tapentadol	tablet extended release 12 hr	50 mg
tramadol	capsule, ER biphase 24 hr	300 mg
tramadol	capsule, ER biphase 24 hr	100 mg
tramadol	capsule, ER biphase 24 hr	150 mg
tramadol	capsule, ER biphase 24 hr	200 mg
tramadol	tablet	50 mg
tramadol	tablet extended release 24 hr	100 mg
tramadol	tablet extended release 24 hr	200 mg
tramadol	tablet extended release 24 hr	300 mg
tramadol	tablet, ER multiphase 24 hr	100 mg

Non-proprietary name	Dosage form/route	Strength
tramadol	tablet, ER multiphase 24 hr	200 mg
tramadol	tablet, ER multiphase 24 hr	300 mg
tramadol	tablet, disintegrating	50 mg
tramadol/acetaminophen	tablet	37 5-325 mg
tramadol/dietary supplement,misc cb 11	combo pack	50 mg
tramadol/glucosamine	suspension for reconstitution	10-5 mg/mL

* Lower dosage strength oral or transmucosal opioid analgesic products were defined as products which, when one unit (e.g. tablet, lozenge) is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result a total daily dose of < 90 MME.

Higher dosage strength oral or transmucosal opioid analgesic products**

Non-proprietary name	Dosage form/route	Strength
buprenorphine	buccal film	300 mcg
buprenorphine	buccal film	450 mcg
buprenorphine	buccal film	600 mcg
buprenorphine	buccal film	750 mcg
buprenorphine	buccal film	900 mcg
fentanyl	buccal film	1200 mcg
fentanyl	buccal film	200 mcg
fentanyl	buccal film	400 mcg
fentanyl	buccal film	600 mcg
fentanyl	buccal film	800 mcg
fentanyl	buccal lozenge on a handle	1200 mcg
fentanyl	buccal lozenge on a handle	1600 mcg
fentanyl	buccal lozenge on a handle	200 mcg
fentanyl	buccal lozenge on a handle	400 mcg
fentanyl	buccal lozenge on a handle	600 mcg
fentanyl	buccal lozenge on a handle	800 mcg
fentanyl	buccal tablet, effervescent	200 mcg
fentanyl	buccal tablet, effervescent	400 mcg
fentanyl	buccal tablet, effervescent	600 mcg
fentanyl	buccal tablet, effervescent	800 mcg
fentanyl	nasal spray,non-aerosol	300 mcg/spray
fentanyl	nasal spray,non-aerosol	400 mcg/spray
fentanyl	sublingual spray,non-aerosol	1200 mcg
fentanyl	sublingual spray,non-aerosol	1600 mcg
fentanyl	sublingual spray,non-aerosol	400 mcg/spray
fentanyl	sublingual spray,non-aerosol	600 mcg/spray
fentanyl	sublingual spray,non-aerosol	800 mcg/spray
fentanyl	sublingual tablet, sublingual	200 mcg
fentanyl	sublingual tablet, sublingual	300 mcg
fentanyl	sublingual tablet, sublingual	400 mcg
fentanyl	sublingual tablet, sublingual	600 mcg
fentanyl	sublingual tablet, sublingual	800 mcg
hydrocodone	oral capsule, oral only, ER 12hr	50 mg
hydrocodone	oral capsule,extended release 12 hr	50 mg
hydrocodone	oral tablet,oral only,ext.rel.24 hr	100 mg
hydrocodone	oral tablet,oral only,ext.rel.24 hr	120 mg
hydromorphone	oral tablet	8 mg
hydromorphone	oral tablet extended release 24 hr	32 mg
methadone	oral concentrate	10 mg/mL
methadone	oral solution	10 mg/5 mL
methadone	oral solution	5 mg/5 mL
methadone	oral syringe	10 mg/mL
methadone	oral syringe	5 mg/5 mL
methadone	oral tablet,soluble	40 mg
morphine	oral capsule, ER multiphase 24 hr	120 mg
morphine	oral capsule, ER multiphase 24 hr	90 mg
morphine	oral capsule,extend.release pellets	100 mg
morphine	oral capsule,extend.release pellets	130 mg
morphine	oral capsule,extend.release pellets	150 mg
morphine	oral capsule,extend.release pellets	200 mg
morphine	oral solution	20 mg/mL
morphine	oral solution	4 mg/mL
morphine	oral syringe	20 mg/mL
morphine	oral tablet	15 mg
morphine	oral tablet	30 mg
morphine	oral tablet extended release	100 mg
morphine	oral tablet extended release	200 mg
morphine	oral tablet extended release	60 mg
morphine	oral tablet,oral only,ext.rel.12 hr	100 mg
morphine	oral tablet,oral only,ext.rel.12 hr	60 mg
morphine	oral tablet,oral only,extnd release	60 mg
morphine/naltrexone	oral capsule,extend.release pellets	100-4 mg
morphine/naltrexone	oral capsule,oral only,ext.rel pell	100-4 mg
oxycodone	oral capsule,sprinkle,ER 12hr tmprr	27 mg
oxycodone	oral capsule,sprinkle,ER 12hr tmprr	36 mg
oxycodone	oral concentrate	20 mg/mL
oxycodone	oral syringe	10 mg/0.5 mL
oxycodone	oral tablet	15 mg
oxycodone	oral tablet	20 mg
oxycodone	oral tablet	30 mg
oxycodone	oral tablet extended release 12 hr	30 mg
oxycodone	oral tablet extended release 12 hr	40 mg
oxycodone	oral tablet extended release 12 hr	60 mg
oxycodone	oral tablet extended release 12 hr	80 mg
oxycodone	oral tablet, oral only	15 mg

Non-proprietary name	Dosage form/route	Strength
oxycodone	oral tablet, oral only	30 mg
oxycodone	oral tablet,oral only,ext.rel.12 hr	30 mg
oxycodone	oral tablet,oral only,ext.rel.12 hr	40 mg
oxycodone	oral tablet,oral only,ext.rel.12 hr	60 mg
oxycodone	oral tablet,oral only,ext.rel.12 hr	80 mg
oxymorphone	oral tablet	10 mg
oxymorphone	oral tablet extended release 12 hr	15 mg
oxymorphone	oral tablet extended release 12 hr	20 mg
oxymorphone	oral tablet extended release 12 hr	30 mg
oxymorphone	oral tablet extended release 12 hr	40 mg
oxymorphone	oral tablet,oral only,ext.rel.12 hr	15 mg
oxymorphone	oral tablet,oral only,ext.rel.12 hr	20 mg
oxymorphone	oral tablet,oral only,ext.rel.12 hr	30 mg
oxymorphone	oral tablet,oral only,ext.rel.12 hr	40 mg
pentazocine/naloxone	oral tablet	50-0.5 mg
tapentadol	oral tablet	100 mg
tapentadol	oral tablet	75 mg
tapentadol	oral tablet extended release 12 hr	150 mg
tapentadol	oral tablet extended release 12 hr	200 mg
tapentadol	oral tablet extended release 12 hr	250 mg

** Higher dosage strength oral or transmucosal opioid analgesic products were defined as products which, when one unit is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result a daily dose of ≥ 90 MME

Transdermal opioid analgesics

Non-proprietary name	Dosage form/route	Strength
buprenorphine	transdermal	5 mcg/hour
buprenorphine	transdermal	7.5 mcg/hour
buprenorphine	transdermal	10 mcg/hour
buprenorphine	transdermal	15 mcg/hour
buprenorphine	transdermal	20 mcg/hour
fentanyl	transdermal	12 mcg/hour
fentanyl	transdermal	25 mcg/hour
fentanyl	transdermal	50 mcg/hour
fentanyl	transdermal	75 mcg/hour
fentanyl	transdermal	100 mcg/hour
fentanyl	transdermal	37.5 mcg/hour
fentanyl	transdermal	62.5 mcg/hour
fentanyl	transdermal	87.5 mcg/hour

Table C2. Products included in analysis of concomitant use in the Sentinel Distributed Database analyses.

Benzodiazepines
alprazolam
alprazolam/dietary suppl.
amitriptyline/chlordiazepoxide
chlordiazepoxide
chlordiazepoxide/clidinium
clobazam
clonazepam
clorazepate dipotassium
diazepam
estazolam
flurazepam
lorazepam
midazolam
oxazepam
quazepam
temazepam
temazepam/dietary suppl.
triazolam
Gabapentinoids
gabapentin
gabapentin/dietary suppl.
pregabalin
Z-Drugs
eszopiclone
zaleplon
zolpidem

Table C3. Nationally estimated number of oral or transmucosal opioid analgesic and transdermal opioid analgesic prescriptions and units* dispensed from U.S. outpatient retail pharmacies 2013 through 2018, annually.

	2013				2014				2015			
	Prescriptions (N)	Share (%)	Units (N)	Share (%)	Prescriptions (N)	Share (%)	Units (N)	Share (%)	Prescriptions (N)	Share (%)	Units (N)	Share (%)
Oral/transmucosal formulations, all dosage strengths	246.3 M	100%	16,703 M	100%	239.0 M	100%	16,202 M	100%	222.3 M	100%	15,252 M	100%
LDSP*	244.1 M	99%	16,529 M	99%	236.9 M	99%	16,045 M	99%	220.5 M	99%	15,115 M	99%
HDSP**	2.2 M	1%	173 M	1%	2.0 M	1%	156 M	1%	1.8 M	1%	137 M	1%
IR oral/transmucosal formulations	233.1 M	95%	15,823 M	95%	225.7 M	94%	15,340 M	95%	209.2 M	94%	14,417 M	95%
LDSP IR formulations	233.0 M	>99%	15,819 M	>99%	225.6 M	>99%	15,335 M	>99%	209.1 M	>99%	14,412 M	>99%
HDSP IR formulations	0.04 M	<1%	4.4 M	<1%	0.04 M	<1%	4.5 M	<1%	0.04 M	<1%	4.6 M	<1%
ER/LA oral/transmucosal formulations	13.3 M	5%	879 M	5%	13.3 M	6%	862 M	5%	13.2 M	6%	836 M	5%
LDSP ER/LA formulations	11.1 M	84%	711 M	81%	11.3 M	85%	710 M	82%	11.4 M	87%	703 M	84%
HDSP ER/LA formulations	2.2 M	16%	169 M	19%	2.0 M	15%	152 M	18%	1.8 M	13%	133 M	16%
Transdermal opioid analgesics	5.4 M	—	58 M	—	5.5 M	—	59 M	—	5.5 M	—	59 M	—

	2016				2017				2018			
	Prescriptions (N)	Share (%)	Units (N)	Share (%)	Prescriptions (N)	Share (%)	Units (N)	Share (%)	Prescriptions (N)	Share (%)	Units (N)	Share (%)
Oral/transmucosal formulations, all dosage strengths	210.9 M	100%	14,479 M	100%	191.7 M	100%	13,052 M	100%	168.7 M	100%	11,174 M	100%
LDSP	209.3 M	99%	14,361 M	99%	190.5 M	99%	12,965 M	99%	167.9 M	>99%	11,117 M	99%
HDSP	1.6 M	1%	118 M	1%	1.2 M	1%	87 M	1%	0.8 M	<1%	58 M	1%
IR oral/transmucosal formulations	198.2 M	94%	13,692 M	95%	180.3 M	94%	12,362 M	95%	158.9 M	94%	10,595 M	95%
LDSP IR formulations	198.1 M	>99%	13,688 M	>99%	180.3 M	>99%	12,360 M	>99%	158.9 M	>99%	10,594 M	>99%
HDSP IR formulations	0.03 M	<1%	3.4 M	<1%	0.02 M	<1%	2.0 M	<1%	0.01 M	<1%	1.3 M	<1%
ER/LA oral/transmucosal formulations	12.7 M	6%	787 M	5%	11.4 M	6%	690 M	5%	9.8 M	6%	579 M	5%
LDSP ER/LA formulations	11.2 M	88%	673 M	85%	10.2 M	90%	605 M	88%	9.0 M	92%	522 M	90%
HDSP ER/LA formulations	1.6 M	12%	114 M	15%	1.2 M	10%	85 M	12%	0.8 M	8%	56 M	10%
Transdermal opioid analgesics	5.1 M	—	53 M	—	4.4 M	—	44 M	—	3.6 M	—	35 M	—

Source: IQVIA National Prescription Audit™. 2013-2018. Data extracted Jan 2019. IR = immediate-release, ER/LA = extended-release or long-acting.
* Units represent one single dosage unit, such as one tablet or one lozenge.
* LDSP = Lower Dosage Strength Products, defined as oral or transmucosal opioid analgesic products for which one unit (e.g. tablet, lozenge) is < 90 MME
** HDSP = Higher Dosage Strength Products, defined as oral or transmucosal opioid analgesic products for which one unit is ≥ 90 MME

Table C4. Nationally estimated number of patients with dispensed prescriptions for oral or transmucosal opioid analgesics or transdermal opioid analgesics dispensed from U.S. outpatient retail pharmacies 2013 through 2018, annually.

	2013		2014		2015		2016		2017		2018	
	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)
Oral or transmucosal opioid analgesics, all dosage strengths	69,236,312	100%	67,332,696	100%	65,009,166	100%	61,857,356	100%	58,050,943	100%	51,564,229	100%
Lower dosage strength products (LDSPs)*	69,153,888	99.9%	67,256,959	99.9%	64,936,626	99.9%	61,790,663	99.9%	57,984,823	99.9%	51,517,177	99.9%
Higher dosage strength products (HDSPs)**	294,011	0.4%	258,741	0.4%	225,201	0.3%	193,819	0.3%	150,267	0.3%	98,045	0.2%
Transdermal opioid analgesics	997,131	—	989,567	—	939,832	—	853,671	—	722,782	—	575,979	—

Source: IQVIA Total Patient Tracker™. 2013-2018, Data extracted January 2019. Sums may add to more than total and percentages may add to more than 100% because patients may have received more than one type of opioid analgesic in a given year. MME was calculated using published conversion factors for each opioid molecule, dosage form, and product.

* Lower Dosage Strength Products (LDSPs) were defined in this analysis as oral or transmucosal opioid analgesic products for which one unit (e.g. tablet, lozenge) is < 90 MME

** Higher Dosage Strength Products (HDSPs) were defined in this analysis as oral or transmucosal opioid analgesic products for which one unit is ≥ 90 MME

Table C5. Number of prescriptions with concomitant use* of selected medications among patients in the Sentinel Distributed Database with claims for oral, transmucosal, or transdermal opioid analgesics, January 2012 through June 2018.

	Any oral or transmucosal opioid analgesic**		Lower dosage strength product (LDSP)***		Higher dosage strength product (HDSP)†		Transdermal opioid analgesic	
Number of prescriptions (N)‡	**373,466,910**	**100%**	**350,546,610**	**100%**	**27,349,071**	**100%**	**13,802,509**	**100%**
Benzodiazepines	90,851,356	24%	82,382,496	24%	10,037,792	37%	4,112,732	30%
Gabapentinoids§	76,378,095	21%	69,950,416	20%	7,751,779	28%	4,302,798	31%
Z-drugs¶	32,229,975	9%	29,458,969	8%	3,327,858	12%	1,445,322	11%
Lower Dosage Strength Product	—	—	—	—	12,112,800	44%	8,326,867	60%

Source: Sentinel Distributed Database, January 2012-June 2018. This data includes the100%* Medicare Fee-for-Service population from 2012 through 2016 and therefore age distributions in this analysis may differ from nationally representative age distributions of patients receiving opioids with an overrepresentation of patients aged 65 years or older.

* Concomitant use assessed for the 7 days prior to, day of, and up to 7 days following a claim for an oral, transmucosal, or transdermal opioid analgesic.

** Totals may sum to more than the total of lower and higher dosage products because patients may have received both a lower and higher dosage product within one calendar year.

*** Lower dosage strength products (LDSPs) were defined in this analysis as oral or transmucosal opioid analgesic products which, when one unit (e.g. tablet, lozenge) is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result a total daily dose of < 90 MME.

† Higher dosage strength products (HDSPs) were defined in this analysis as oral or transmucosal opioid analgesic products which, when one unit is taken at the lowest frequency based on dosing interval according to the FDA-approved label, would result a daily dose of ≥ 90 MME.

‡ Multiple pharmacy claims for a particular opioid on the same day for a patient were de-duplicated into only one claim

§ Gabapentinoids included gabapentin and pregabalin

¶ Z-drugs included eszopiclone, zaleplon, and zolpidem.

8.4. Appendix D. Pubmed search strategy for studies of opioid dose and risk of abuse, addiction, overdose, and death

1. Begin with articles that appear in the results of all of the following four search strings (4070 articles)

a. **Search** analgesics opioid[tiab] OR opioid[tiab] OR alfentanil[tiab] OR alphaprodine[tiab] OR acetylcodeine[tiab] OR alphaprodine[tiab] OR azidomorphine[tiab] OR buprenorphine[tiab] OR butorphanol[tiab] OR cyclazocine[tiab] OR ciramadol[tiab] OR codeine[tiab] OR dezocine[tiab] OR dihydrocodeine[tiab] OR dextromoramide[tiab] OR dextropropoxyphene[tiab] OR diamorphine[tiab] OR diconal[tiab] OR dihydrocodeine[tiab] OR dihydroetorphine[tiab] OR dihydromorphine[tiab] OR dimethylthiambutene[tiab] OR dipipanone[tiab] OR eptazocine[tiab] OR ethylmorphine[tiab] OR fentanyl[tiab] OR hydrocodone[tiab] OR hydromorphone[tiab] OR ketobemidone[tiab] OR levorphanol[tiab] OR meperidine[tiab] OR morphine[tiab] OR nalbuphine[tiab] OR norbuprenorphine[tiab] OR nordextropropoxyphene[tiab] OR normorphine[tiab] OR norpethidine[tiab] OR norpropoxyphene[tiab] OR oxycodone[tiab] OR oxymorphone[tiab] OR opiate[tiab] OR oripavine[tiab] OR opium[tiab] OR pentazocine[tiab] OR propoxyphene[tiab] OR piritramide[tiab] OR profadol[tiab] OR tapentadol[tiab] OR tilidine[tiab] OR tramadol[tiab] OR trimeperidine[tiab]. (143477)

b. **Search** (“opioid-related disorders”[tiab] OR misuse[tiab] OR abuse[tiab] OR overdose[tiab] OR “drug overdose”[tiab] OR death[tiab] OR “death rate”[tiab] OR mortality[tiab] OR disability[tiab] OR function[tiab] OR “recovery of function”[tiab] OR “function recovery”[tiab] OR “function recoveries”[tiab] OR OR “adverse event”[tiab] OR “adverse events”[tiab] OR “adverse drug event”[tiab] OR “adverse drug events”[tiab] OR “drug toxicity”[tiab] OR “drug toxicities”[tiab] OR “side effect”[tiab] OR “side effects”[tiab] OR “adverse drug reaction”[tiab] OR “adverse drug reactions”[tiab] OR “adverse outcome”[tiab] OR “adverse outcomes”[tiab] OR morbidity[tiab] OR mortality[tiab] OR “substance-related disorders” [mesh] OR "analgesics, opioid/poisoning" [mesh] OR "analgesics, opioid/adverse effects"[Mesh] OR "analgesics, opioid/toxicity"[Mesh] OR ("analgesics, opioid/administration and dosage"[MeSH] AND ("Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "prescription drug misuse"[Mesh] OR "acute Disease"[Mesh] OR "chronic Disease"[Mesh] OR "mortality"[Mesh] OR "opioid-related disorders"[Mesh] OR "drug overdose"[Mesh] OR "death"[Mesh]) [370723]

c. **Search** dose[tiab] OR doses[tiab] OR dosage[tiab] OR dosage-strength [tiab] OR “dosage strength” [tiab] OR high-strength [tiab] OR “high strength” [tiab] OR opioid-tolerant [tiab] OR “opioid tolerant” [tiab] OR “opioid tolerance” [tiab]OR dosing[tiab] OR "dose response"[tiab] OR "dose responses"[tiab] OR "dose-response"[tiab] OR "dose-responses"[tiab] (1362878)

2. **Restrict the search results in #1 to relevant article types (5,127 articles):**

   a. **Search** ("systematic review"[tiab] OR cohort[tiab] OR "case-control"[tiab] OR database[tiab] OR datalink[tiab] OR "claims data"[tiab] OR "drug utilization"[tiab] OR "electronic health records"[tiab] OR "electronic medical records"[tiab] OR biobank[tiab] OR "pooled analysis"[tiab] OR crossover[tiab] OR "registry"[tiab] OR "registries"[tiab] OR meta-analysis[tiab] OR retrospective[tiab] OR prospective[tiab] OR "cross sectional"[tiab] OR "cross-sectional"[tiab] OR "prevalence study"[tiab] OR "longitudinal study"[tiab] OR "before-after study"[tiab] OR "administrative database"[tiab] OR "insurance claim"[tiab] OR "matched-cohort"[tiab] OR "population-based"[tiab] OR "insurance database"[tiab] OR "claims database"[tiab] OR

"pharmaceutical claims"[tiab] OR "case control"[tiab] OR "meta analysis"[tiab] OR self-controlled[tiab] OR "self controlled"[tiab] OR comparative[tiab] OR EMR[tiab] OR prevalence[tiab] OR incidence[tiab] OR rate[tiab] OR "administrative claim"[tiab]) **DOWN TO** 1310

b. Exclude animal studies from the search results in #2 (4,987 articles): NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))
DOWN TO 1217

c. Exclude from the search results in #4 any preclinical studies or genetics studies (635 articles): cell[tiab] OR "cell line"[tiab] OR cellular[tiab] OR tissue[tiab] OR"in vitro"[tiab] OR spectroscopic[tiab] OR spectrometer[tiab] OR spectrophotometry[tiab] OR "transformation products"[tiab] OR synthesized[tiab] OR "gene variants"[tiab] OR polymorphism[tiab] OR plant[tiab]

DOWN TO 1175

d. Exclude from the search results in #5 any studies of pharmacodynamics or pharmacokinetics (604 articles): Search pharmacokinetics[tiab] OR pharmacokinetic[tiab] OR pharmacodynamic[tiab] OR pharmacodynamics[tiab]
DOWN TO 1111

e. Exclude from the search results in #6 any articles that are explicitly not epidemiology studies (302 articles): Search autobiography[tiab] OR bibliography[tiab] OR biography[tiab] OR books[tiab] OR "case reports" [tiab] OR "clinical conference"[tiab] OR "clinical trial"[tiab] OR "phase I"[tiab] OR "phase II"[tiab] OR "phase III"[tiab] OR comment[tiab] OR "consensus development"[tiab] OR "controlled clinical trial"[tiab] OR editorial[tiab] OR interview[tiab] OR news[tiab] OR newspaper[tiab] OR "patient education handout"[tiab] OR OR "randomized controlled" [tiab] OR "randomised controlled"[tiab] OR "case series"[tiab] OR "case-series"[tiab] OR webcast[tiab] OR Addresses[ptyp] OR Autobiography[ptyp] OR Bibliography[ptyp] OR Biography[ptyp] OR pubmed books[filter] OR Case Reports[ptyp] OR Clinical Conference[ptyp] OR Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Comment[ptyp] OR Congresses[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR Controlled Clinical Trial[ptyp] OR Dictionary[ptyp] OR Directory[ptyp] OR Editorial[ptyp] OR OR Guideline[ptyp] OR Historical Article[ptyp] OR Interactive Tutorial[ptyp] OR Interview[ptyp] OR Lectures[ptyp] OR Legal Cases[ptyp] OR Legislation[ptyp] OR OR News[ptyp] OR Newspaper Article[ptyp] OR Review[ptyp]
DOWN TO 633

f. Exclude from the search results in #7 articles that have a MeSH term indicating that they focus on either of the following: side effects unrelated to overdose or abuse, palliative care, or naloxone (242 articles): Search "opiate substitution treatment" [mesh] "palliative care" [mesh] OR "terminally ill"[mesh] OR "cancer pain" [mesh] OR "naloxone" [mesh] OR "constipation/chemically induced"[mesh] OR "constipation/diagnosis" [mesh] OR "constipation/epidemiology"[mesh] OR "constipation/psychology"[mesh] OR "analgesia, epidural"[mesh]
DOWN TO 495

g. Restrict the search results in #8 to articles published in English (235 articles): Filter: English
DOWN TO 456

h. Restrict the search results in #3 to articles entered in PubMed 1/1/2008 – 12/31/2018 (664 articles): "2009/01/01"[Date - Entrez] : "12/31/2018"[Date – Entrez]

DOWN TO 259

8.5. Appendix E. Literature review of observational epidemiologic studies examining opioid dose and the risk of abuse and addiction

Abbreviations are defined at the end of the appendix.

First Author, Year	Data Type	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
Coutinho, 2018[18]	Truven Health MarketScan (Administrative claims)	Retrospective cohort with Classification and Regression Tree (CART) Analysis	Adults (n=21,072) age ≥18 yrs, 2007-2011, with commercial insurance or Medicare, (Truven Health MarketScan) with chronic opioid Rx for CNCP Inclusion criteria: - ≥3 nondiagnostic medical claims for pain condition, ≥1 and <12 mos apart, and no malignancy dx from 12 mos before first pain dx date onward - ≥90 days' supply of any C2, 3, 4 opioid within 6 mos of initial pain dx -continuous medical coverage ≥12 mos before first CNCP dx date and ≥12 mos after index date	Grouped by avg. daily dose, age, and (some groups) days' supply The model produced 7 terminal nodes, of which 4 represented sub-groups which substantially elevated risk of opioid abuse. Node 1: MME≤62 3, age≤34.5 Node 3 (3.8%): MME≤62.3, age>34.5, days' supply>364 Node 5 (10%): MME>62.3, age≤46.5, Node 7 (5.3%): MME>62.3, age>46.5, days' supply>328	Diagnosis of opioid abuse after receipt of opioid Rx: ICD-9-CM codes 304.0, 304.7, 305.5, 965.0 (excluding 965.01)	Final tree using full study value: AUC=0.78, Se=0.703, Sp=0.741, PPV=0.056 (% with opioid abuse dx) OR training data, OR validation data Node 1: (4 3%) 16 (11, 22); 10 (7,14) Node 3: (3.8%) 6 (3, 10); 3 (1.4, 5) Node 5: (10%) 16 (11, 22); 10 (7, 14) Node 7: (5 3%) 8 (5, 12); 3 (2, 5)	Classification And Regression Tree (CART) Analysis to group patients by their risk for opioid abuse No validation of outcome Used only dose, days' supply, and age to classify abuse risk.

First Author, Year	Data Type	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
Brat, 2018[16]	Aetna Health Insurance (Administrative claims)	Retrospective cohort	Commercially insured adults (N=1,015,116) age ≥18 yrs, 2008-early 2016 Inclusion criteria: -Surgery with prior medical coverage ≥6 m, prior pharmacy coverage ≥3, plus post-surgery medical coverage ≥1 yr & pharmacy coverage ≥90 days -"total opioid use" ≤7 days during 60 days before surgery - first eligible surgery was included if >1 surgery Exclusion criteria: ICD-9 code for opioid / unspecified drug abuse, dependence, overdose, or disorder, in 6 m before surgery	10 MME/day increments in daily dose above 1-19. Note: patients with no opioids appeared to have been included in reference group (See Table 1).	ICD-9 claim for Opioid dependence, abuse, or overdose/poisoning, comprising codes for prescription opioids only	Each 10 MME/day increment in daily dose above <20: adjusted HR=1.008 (1.003-1.013), Duration of use modified the association	Cox Proportional Hazards model adjusted for: duration of use, sex, age, surgery year, state, surgery type, API of opioid rx, benzodiazepine rx, comorbidity diagnosis codes (psychiatric, non-cancer pain, morbid obesity)
Ciesielski, 2016[17]	Pharmacy and Medical Benefit Data from Express Scripts,	Retrospective cohort	Commercially-insured adults (N=694,851) age≥18 yrs, ≥1 Rx	1-119 (ref), ≥120	ICD-9 Claim for opioid abuse (304.0x) or dependence	≥120 vs. 1-119 (ref) adjusted OR=1.98 (1.68-2.34)	Logistic regression adjusted for gender, age, region of

First Author, Year	Data Type	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
	a Pharmacy Benefit Manager (Administrative claims)		opioid claim during 10/1/2011 – 9/30/2012, continuous enrollment in 12 mos before and 12 mos after claim date (index date) Excluded: cancer diagnosis, chemotherapy, antiemetics Rx, LT care facility, hospice/palliative/EOL care, prior opioid dependency dx, buprenorphine or naloxone Rx		(305.5x) (N=2,067, 0.3%)	Opioid days' supply >90 days (vs. ≤90 days' supply or no opioid Rx) during 6 mos before index date: OR=4.39 (3.71-5.19)	country, prior mental illness, non-opioid substance abuse, alcohol abuse, tobacco use disorder, doctor shopping, pharmacy shopping, distance from patient to prescriber, # prior opioid Rx, >50% of opioids dispensed were IR if they received opioid Rx ≥6 mos. of pre-period (-) the opioid days' supply analysis used people with no opioid Rx in the reference group
Edlund, 2014[48]	HealthCore Integrated Research Database (Administrative claims)	Retrospective cohort	Adults with a newly-diagnosed chronic pain condition (N=568,640)	0 (ref), 1-36, 37-120, >120 (high) Duration: 0, 1-90 (acute), >91 days (chronic)	ICD-9-CM codes for opioid abuse or dependence(N=497)	1-36 MME/day Acute OR 3.03, CI: 2.32-3.95 Chronic OR 14.92, CI: 10.38-21.46 37-120 MME/day Acute OR 2.80, CI: 2.12-3.71 Chronic OR 28.69, CI: 20.02-41.13 >120 MME/day	Overlapping exposure and outcome time windows—unable to establish temporality

First Author, Year	Data Type	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
						Acute OR 3.10, CI: 1.67-5.77 Chronic OR 122.45, CI: 72.79-205 99	
Edlund, 2010[49]	HealthCore Integrated Research Database and Arkansas Medicaid (both Administrative claims)	Retrospective cohort	Commercially-insured (N=36,605) and Medicaid (N=9,651) adults with 90 continuous days of opioid use within 6 months	<Median (ref), Median-120, >120 Median Commercially-insured: 32 Medicaid: 35	Diagnosis of opioid abuse or dependence, defined by ICD-9 codes(N=1,188 in the commercially-insured cohort; N=277 in Medicaid cohort)	Commercially-insured Median-120 MME/day OR 1.48, CI: 1.27-1.72 >120 MME/day OR 2.19, CI: 1.74-2.74 Medicaid >120 MME/day OR 1.70, CI: 1.07-2.70	Overlapping exposure and outcome observation time windows—unable to establish temporality
Sullivan, 2010[50]	HealthCore Integrated Research Database and Arkansas Medicaid (both Administrative claims)	Retrospective cohort	Commercially-insured (N=21,685) and Medicaid (N=10,159) adults on opioids >90 days over six months	<Median (ref), Median-119, >120 Median Commercially-insured: 31 Medicaid: 35	Opioid misuse score, calculated by the authors from # prescribers, # pharmacies, # days' supply of IR opioid analgesics, and # days' supply of ER opioids. Misuse score was then categorized. Highest category of opioid misuse was "probable misuse" (N	Commercially-insured Possible misuse: >120 MME/day OR 2.37, CI: 2.13-2.65 Probable misuse: >120 MME/day OR 6.70, CI: 5.60-8.03 Medicaid	Overlapping exposure and outcome time windows—unable to establish temporality

First Author, Year	Data Type	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
					= 276 in commercially-insured cohort; N = 41 in Medicaid cohort). Intermediate category of misuse was "possible misuse" (N =480 in commercially-insured cohort; N = 124 in Medicaid cohort).	Possible misuse: >120 MME/day OR 2.02, CI: 1.61-2.54 Probable misuse: >120 MME/day OR 4.69, CI: 3.03-7.24	
Braden, 2010[51]	HealthCore Integrated Research Database and Arkansas Medicaid (both Administrative claims)	Retrospective cohort	Commercially-insured (N=38,491) and Arkansas Medicaid (N=10,159) adults on opioids ≥90 days	<Median (ref), Median-120, >120 Median Commercially-insured: 32 Medicaid: 35	Emergency department (ED) visits (N=9,297 in commercially-insured cohort; N=2,863 in Medicaid cohort) and alcohol and drug-related encounters (ADEs, N=622 in commercially-insured cohort; N=264 in Medicaid cohort)	Commercially-insured ED visits: Median-120 MME/day RR 1.30, CI: 1.26-1.34 >120 MME/day RR 1.08, CI: 1.02-1.15 ADEs: Median-120 MME/day RR 1.66, CI: 1.35-2.03 >120 MME/day RR 2.18, CI: 1.28-3.00 Medicaid ADEs: >120mg MED daily	Overlapping exposure and outcome time windows—unable to establish temporality

First Author, Year	Data Type	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
						RR 2.06, CI: 1.15-3.67	

ADE, alcohol- and drug-related events; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; AUC, area under the curve; CART, Classification and Regression Tree analysis; CI, confidence interval; CNCP, chronic non-cancer pain; Dx, diagnosis; EOL, end-of-life; ER, extended-release; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Clinical Modification; IR, immediate-release; LA, long-acting; LT, long-term; MA, Massachusetts; MED, morphine-equivalent dose; MME, morphine milligram-equivalents; NDI, National Death Index; OR, odds ratio; Rx, prescription; Se, sensitivity; Sp, specificity; SUD, substance use disorder; WA, Washington

8.6. Appendix F. Literature review of observational epidemiologic studies examining opioid dose and the risk of fatal and nonfatal overdose

Abbreviations are defined at the end of the appendix.

First Author, Year	Data	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
STUDIES OF FATAL OPIOID OVERDOSE AS MEASURED IN CAUSE-OF-DEATH DATA							
Rose, 2018[36]	Data linkage from (1) Massachusetts (MA) Prescription Drug Monitoring Program, (2) MA All-Payer Claims Database, (3) MA mortality data	Retrospective cohort	Adults age ≥18 yrs who filled ≥1 opioid Rx in MA, 2011-15. Excluded: claim for regionally or distantly disseminated cancer; received buprenorphine or methadone for MAT; date of death before date of first fill.	≥100 in ANY 3 months of the study period (relative to ≥100 MED in <3 months OR <100 MED)	1) Fatal opioid overdose (from cause-of-death data) 2) Non-fatal opioid overdose (from ICD-9 and ICD-10 claims codes). If multiple overdoses recorded, used first one. 3) All-cause mortality	Fatal overdose aHR=2.22 (1.99-2.48) Non-fatal overdose aHR=1.68 (1.59-1.76) All-cause mortality aHR=2.18 (2.14-2.23)	Adj for age, sex, community-level poverty rate, depression, alcohol use disorder, rural town of residence, Elixhauser comorbidity index, benzodiazepine overlap ≥3 mos, ≥4 prescribers, ≥4 pharmacies, ≥3 cash payments, no pain diagnosis
Holt, 2018[35]	Data linkage from (1) Maine Prescription Drug Monitoring Program and (2) Vital Statistics Mortality Records	Case-control	Cases: Decedents with primary or contributing cause of death from controlled substance overdose, ME, 2006-10. Matched Controls: matched on age, gender, county; had	Among 480 cases and unknown number of controls with an opioid prescription, Maximum opioid MED in 90 days before death (index date): 1-24 (ref.), 25-	Fatal drug overdose: primary or contributing cause of death from controlled substance overdose,	Crude OR: 25-99: 1.1 100-199: 3.7, 200-299: 11.0, 300-399: 14.1,	Reported crude ORs, which is not valid in a matched case-control study because the matching creates bias that must be adjusted for in the model.

First Author, Year	Data	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
			≥1 record in ME PDMP in year preceding date of case's death	99, 100-199, 200-299, 300-399, ≥400.		≥400: 19.0	30.4% of cases were drug overdose deaths from other prescription drugs, not opioids.
Garg, 2017[33]	Washington (WA) Medicaid pharmacy and medical claims, WA Death Certificates	Retrospective cohort	18-64 years old, Enrolled WA Medicaid fee-for-service≥90 d, ≥1 opioid claim in 2006-10. (n=150,821) Excluded: hx cancer, cancer claim in yr following opioid, recent MAT. Censored if MAT, cancer dx	1-19 (ref), 20-49, 50-89, 90-119, 120-199, ≥200	Fatal opioid overdose, death cert did not mention heroin (n=316, rate: 125.8/100,000 person-years)	1-19 (ref), 20-49 aHR=1.2 (0.7-2.1), 50-89 aHR=2.3 (1.4-4.1), 90-119 aHR=4.0 (2.2-7.3), 120-199 aHR=3.8 (2.1-6.9), ≥200 HR=4.9 (2.9-8.1)	Adj for age, sex, race/ethnicity, area of residence, Charlson index, use of sedative-hypnotics, IR/ER OA
Bohnert, 2016[38]	VA pharmacy and medical claims; National Death Index (NDI) linkage	Matched case-control study	Veterans who started Rx opioid analgesic for 1st time in 2 years during FY02-09; VA patients during FY04-09; current OA Rx on the date of case's death; chronic, non-cancer pain diagnosis in FY04-09; no hospice. Cases: unintentional/undetermined. fatal Rx opioid overdose (N=221)	Continuous value of daily dose, MME, for Rx that was current on date case died (same date for matched control)	Fatal opioid overdose ruled unintentional or undetermined (N=221)	Daily dose Mean, Median: Cases: 98.1, 60 Controls: 60.0, 25 *Note that means and medians are unadjusted, but controls were matched to cases. This may have inflated the controls' means and medians.* (Did not report aOR)	Modeled dose as a continuous variable. Did not test for a linear relationship. Adjusted for variables measured in year before the most recent new opioid analgesic Rx: age, sex, race/ethnicity, substance use disorder dx, depression dx, other psych dx, acute pain condition, chronic dx,

First Author, Year	Data	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
			Matched controls: living patients on the date of the case's death (N=221)			AUC=0.71 (0.66-0.76), from adjusted logistic regression Sensitivity and Specificity of fatal overdose for dose, 10 MME increments. 90 MME: Se=0.33, Sp=0.88, LR=2.67, suggesting low utility as clinical cut-off. Increasing risk observed with increasing doses, but no clear cut-off.	Charlson index, benzodiazepine Rx, antidepressant Rx, anticonvulsant Rx, continuous opioid analgesic Rx in 90 d before index date
Ilgen, 2016[31]	Data linkage of (1) VA claims, 2004-2005, and (2) NDI cause-of-death data	Case-Control	VA Patients in 2004-05 with chronic pain dx and treated with opioid analgesics Exclusion criteria: palliative care, hospice Controls: random sample of population described above (N=123,414) Cases: intentional, fatal overdose during 2004-2009 (N=532)	1-19 (ref), 20-49, 50-99, ≥100	Intentional, fatal overdose, any substance, using ICD-10 codes X60-X69	20-49: aHR=1.59 (1.12-2.27) 50-99: aHR=1.74 (1.09-2.76) ≥100: aHR=2.09 (1.22-3.56)	Adjusted for: age, race, race/ethnicity, specific diagnosis codes for: SUD, depression, various other psychiatric, pain, and other medical conditions
Dasgupta, 2016[8]	North Carolina PDMP linked to state vital statistics cause-of-death data	Retrospective cohort	North Carolina residents dispensed a prescription for transdermal or oral solid opioid analgesic (codeine,	1-39 (ref.), 40-59, 60-79, 80-99, 100-119, 120-139, 140-159, 160-179, 180-	Fatal opioid overdose (N=629)	Unadjusted incidence rate ratio of fatal overdose increased with increasing daily	Results were crude incidence rate ratios since there were no covariate data

First Author, Year	Data	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
			hydrocodone, hydromorphone, fentanyl, methadone, morphine, oxycodone, oxymorphone) in 2010 (N=2,182,374)	199, 200-249, 250-299, 300-349, 350-399, 400-499, 500-5,000		dose until ~200 MME/day, then leveled off.	available for adjustment.
Park, 2015[28]	Data linkage of (1) VA claims, 2004-2009, and (2) NDI cause-of-death data	Case-cohort	Cases: Veterans with fatal drug overdose while receiving opioid analgesics in fiscal year (FY) 2004-0 (N=2,400) Controls: 5% annual random sample of veterans dispensed opioids in FY 2004-09 (N=420,386)	0-19 (ref), 20-49, 50-99, ≥100	Any fatal drug overdose (N=2,400)	20-49 MME/day aHR 1.57, CI: 1.28-1.91 50-99 MME/day aHR 2.81, CI: 2.26-3.50 ≥100 MME/day aHR 3.30, CI: 2.62-4.16	Adjusted for age, sex, race/ethnicity, area-level poverty, Charlson comorbidity index, SUD dx, recent hospital admission related to SUD, depression dx, PTSD dx, bipolar or psychotic disorder dx, cancer dx, use of other drugs
Baumblatt, 2014[24]	TN PDMP and state vital records	Matched case-control	Cases: Tennessee residents with fatal opioid overdose and had 1+ record in the Tennessee Controlled Substances Monitoring Program in 2009-2010 (N=592) Controls: Tennessee residents dispensed opioids who were alive in 2009-2010 (1:20 age- and sex-matched controls, N=11,840)	<20 (ref), 20-40, 41-80, 81-100, 101-200, 201-400, >400	Fatal opioid overdose (N=592)	≥100 MME/day aOR 11.2, CI: 8.3-15.1	Adjusted for # of prescribers and # of pharmacies; there was no other information on potential confounders since this study used PDMP data and cause-of-death data.
Paulozzi, 2012[23]	NM PDMP and state vital records	Matched case-control	Cases: New Mexico residents who died of Rx	Average MME/day during the 6 months	Unintentional, fatal drug overdose	41-120 MME/day	Multivariable model included age and sex.

First Author, Year	Data	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
			drug overdose and had 1+ records in the New Mexico Prescription Monitoring program (PMP) (N=300) Controls: New Mexico in the PMP file with 1+ prescription during the 6 months prior to the date of death of the matched case. (N=5,993)	prior to the cases death (same period for matched controls). 0-40 (ref), 41-120, >120	(N=300)	aOR 12.2, CI: 9.2-16.0 >120 MME/day aOR 11.3, CI: 8.1-15.8	Inclusion of 0 MME/day in the reference category makes it challenging to interpret the ORs. Cases included an unknown number of fatal overdoses from rx drugs
Bohnert, 2011[22]	VA pharmacy dispensing and EMR data, linked to NDI cause-of-death data	Case-cohort	Cases: Veterans with fatal opioid overdose while receiving opioid analgesics in fiscal year (FY) 2004-08 (N=750) Cohort: 5% annual random sample of veterans dispensed opioids in FY 2004 and 2005 (N=154,684)	0, 1-19 (ref), 20-49, 50-99, ≥100	Fatal opioid overdose that was ruled unintentional or undetermined (N=750)	≥100mg MME/day *Substance use disorder patients* aHR 4.54, (2.46-8.37) *Chronic pain patients* aHR 7.18, CI: 4.85-10.65	Multivariable model adjusted for age, sex, race/ethnicity, opioid fill that was regularly-scheduled vs. as-needed, pain-related diagnoses, psychiatric diagnoses, COPD, CVD, sleep apnea dx
Gomes, 2011[20]	Ontario prescription records and province vital records, 1997-2006	Case-control	Ontario men and women, age 15-64, who qualified for public prescription drug insurance and who were dispensed an opioid for non-cancer pain, 1997-2006 (N=498 cases and N=1,714 matched controls)	1-19 (ref), 20-49, 50-99, 100-199, >200	Opioid-related death, defined as death caused by a drug combination containing at least one opioid, or death in which a toxicological analysis determined an opioid concentration high enough to produce	20-49 MME/day aOR 1.32 (0.94-1.84) 50-99 MME/day aOR 1.92 (1.30-2.85) 100-199 MME/day aOR 2.04 (1.28-3.24) ≥200 MME/day	Multivariable model adjusted for disease risk index, age, sex, index year, comorbidity index

First Author, Year	Data	Study Design	Population	Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)	Outcome	Notable Findings (95% Confidence Interval)	Comments
					death (N=498); definition includes intentional overdose	aOR 2.88 (1.79-4.63)	
Gomes, 2011[21]	Ontario prescription records and province vital records, 2004-2006	Retrospective cohort	Ontario men and women, age 15-64 in 2004, who qualified for public prescription drug insurance and who received a prescription for an opioid in 2004 (N=154,411)	1-200, 201-400, >400	Opioid-related death during (N=302), defined as death caused by a drug combination containing at least one opioid, or death in which a toxicological analysis determined an opioid concentration high enough to produce death.	*Two-year, opioid-related standardized mortality rates per 1,000 population* ≤200 MME/day 1.63 (1.42-1.85) 201-400 MME/day 7.92 (5.25-11.49) >400 MME/day 9.94 (2.78-25.12)	Two-year Opioid-related mortality rates standardized by age and sex
STUDIES OF OVERDOSE MEASURED BY CLAIMS DATA (NON-FATAL OVERDOSE, SOME ALSO INCLUDED FATAL OVERDOSE)							
First Author, Year	**Data**	**Study Design**	**Population**	**Exposure (Daily dose in morphine milligram equivalents (MME) except where noted)**	**Outcome**	**Notable Findings (95% Confidence Interval)**	**Comments**
Rose, 2018[36]	Data linkage from (1) MA Prescription Drug Monitoring Program, (2) MA All-Payer Claims Database, (3) MA mortality data	Retrospective cohort	Adults age ≥18 yrs who filled ≥1 opioid Rx in MA, 2011-15. Excluded: claim for regionally or distantly	≥100 in ANY 3 months of the study period (relative to ≥100 MED in <3 months OR <100 MED)	1) Fatal opioid overdose (from cause-of-death data) 2) Non-fatal opioid overdose (from ICD-	Fatal overdose aHR=2.22 (1.99-2.48)	Multivariable model included age, sex, community-level poverty rate, depression, alcohol use disorder, rural town of residence, Elixhauser comorbidity index, benzo

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			disseminated cancer; received buprenorphine or methadone for MAT; date of death after date of first fill.		9 and ICD-10 claims codes). If multiple overdoses recorded, used first one. 3) All-cause mortality	Non-fatal overdose aHR=1.68 (1.59-1.76) All-cause mortality aHR=2.18 (2.14-2.23)	overlap ≥3 mos, ≥4 prescribers, ≥4 pharmacies, ≥3 cash payments, no pain diagnosis
Nadpara, 2018[37]	PharMetrics Plus: health and pharmacy claims, from U.S. patients, primarily commercially-insured	Case-control	Inclusion criteria: Patients age ≥18 y with ≥1 opioid pharmacy claim, 2009-2013, and ≥6 mos. enrollment pre-index date Cases: (N=7,234) serious opioid-induced respiratory depression (first occurrence =index date) Controls: (N=28,932) no serious OIRD, matched to case by index date	Maximum MED during 6 months pre-index date: 1-19 (ref), 20-49, 50-99, ≥100	Serious opioid-induced respiratory depression, defined by an algorithm that used ICD-9 claims codes and CPT codes. ICD-9 codes for poisoning involving prescription opioid plus one of the following: an adverse effect code for life-threatening respiratory or CNS depression, or a CPT procedure code for mechanical ventilation or critical care	20-49: aOR=0.96 (0.81-1.15) 50-99: aOR=1.35 (1.13-1.62) ≥100: aOR=2.31 (1.90-2.81)	Multivariable model included age, sex, census region, medical comorbidities including cancer, pain diagnoses, SUD, psychiatric comorbidities, concomitant medications, opioid active ingredient, opioid formulation, ED visit, hospitalization *Included patients with cancer diagnosis*

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Oliva, 2017[34]	Data linkage from (1) VA EHR and (2) NDI cause-of-death	Case-control	1,135,601 VA patients with an outpatient opioid analgesic prescription in FY2010 (Oct 2009-Sept 2010) and either EHR data on VA medical encounter in 2011 or cause-of-death Cases: occurrence of composite outcome (column after next one) in FY2011 (N=23,790) Controls: in FY2011, did not have outcome in FY2011 and had a VA medical encounter	Linear variable for 90th percentile of patient's MED in 2010.	Any overdose or suicide-related event, defined as a claim for any drug overdose, suicide attempt, or suicidal ideation, or death due to drug overdose or suicide (NDI ICD-10 code)	0.3% increase in risk with each additional MED in multivariable-adjusted model	Multivariable model included age, sex, duration of opioid therapy, opioid form, concomitant sedative medications, history of overdose or suicide attempt/ideation, substance use dx, mental illness dx, medical comorbidities
Cochran, 2017[32]	Pennsylvania Medicaid pharmacy and medical claims	Retrospective cohort	Adults 18-64 yrs old who had ≥1 opioid claim in Pennsylvania Medicaid pharmacy benefit in 2007-12, after ≥6 months enrollment without an opioid Rx or diagnosis of OUD or OD (N=372,347 patients). Excluded: any cancer claim, hospice, LT care ≥90 d.	1-19 (ref), 20-49, 50-99, ≥100	ICD-9 code for opioid poisoning (1,270 overdose events out of 583,013 treatment episodes. Treatment episode = period with ≥1 opioid claim; multiple claims included in 1 episode if gap between claims <6 mos)	Calculated adjusted rate ratios: 20-49 aRR=1.02 (0.85-1.23), 50-99 aRR=1.26 (0.97-1.63), ≥100 aRR=1.96 (1.36-2.83) Calculated adjusted risks: 1-19: 0.29%, 20-49: 0.30% ,	Multivariable model included age, sex, race/ethn, urban/rural, type of eligibility; prior: benzo Rx, muscle relaxant Rx, comorbitidies; abuse claims during the episode ≥7 days before OD, dr/pharmacy shopping index, methadone during episode before OD, buprenorphine during episode before OD

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						50-99: 0.37%, ≥100: 0.59%	
Dilokthornsakul, 2016[30]	Colorado Medicaid pharmacy and medical claims	Case-control	Adults age 18-64 yrs, enrolled in Colorado Medicaid ≥1 year before OD (same date used for matched control)	1-50 (ref), >50	ED visit or hospitalization with ICD-9 coded opioid overdose (n=816)	>50 aOR=1.99 (1.51-2.61)	Multivariable model included age, sex, dispensed opioid<30 days of case index date (y/n). Variables measured in year before OD: benzodiazepine Rx, drug/alcohol abuse dx, psych dx, other comorbidities, Charlson comorbidity index, # pharmacies, # prescribers
Larochelle, 2016[29]	Optum database of U.S.. commercial health insurance claims from inpatient, outpatient, and pharmacy	Retrospective cohort	Commercially-insured U.S. adults (N=3,379), age 18-64, with an index claim for opioid overdose that occurred on a date when they had supply of opioid that was at least their third opioid dispensing within the past 84-204 days, ≥90 days prior enrollment, and no cancer dx.	0 (ref), 1-49, 50-99, ≥100	Non-fatal overdose (n=212) from ICD-9 codes from ED or inpatient claims (*repeat* overdose since all patients had ≥ prior overdoses).	Two-year cumulative incidence of repeat overdose from multivariable model: overall 7%; 0: 8% (6-11%) 1-49: 9% (6-14%) 50-99: 15% (10-21%) ≥100: 17% (14-20%)	Multivariable model included age, sex, time-varying current dispensing of buprenorphine or benzodiazepine, pre-index dx of SUD or mental illness, pre-index opioid dose
Liang, 2015[27]	Administrative claims of medical	Retrospective cohort	Commercially-insured, U.S. adults (N=206,869) who filled ≥2 opioid	Average daily dose over 6-month period:	Overdose of any drug, determined by ICD-9 codes	*Relative to 0 MME/day,*	Multivariable model included age, sex, region, pain conditions, mental

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	and pharmacy benefits, Aetna HMO		prescriptions (schedule II or III) for non-cancer pain, 1/2009 – 7/2012, and did not have both a Rx for MAT and a claim for opioid dependence	0 (ref), 1-19, 20-49, 50-99, ≥100 **And** Total MME dispensed (over 6-months/183 days): 0 (ref), 1-1830, >1830	(N=1,385)	*≤1,830 MME total* ≥100 MME/day, ≤1,830 MME total: aOR=3.10 (2.14-4.49) ≥100 MME/day, >1,830 MME total: aOR=2.56 (2.12-3.09)	health and substance abuse conditions, days' supply of benzodiazepines, zolpidem, and antidepressants
Turner, 2015[26]	Administrative claims	Retrospective cohort	Commercially-insured adults (N=206,869) who filled ≥2 opioid prescriptions for non-cancer pain, 1/2009 – 7/2012, and did not have both a Rx for MAT and a claim for opioid dependence	Average daily dose over 6-month period and depression diagnosis during 6-month period or earlier: 0 depression (ref), 0 no depression, and so on for combined categories of depression and 1-19, 20-49, 50-99, ≥100	Overdose of any drug, determined by ICD-9 codes (N=1,385)	*Relative to 0 MME/day, no depression* ≥100 MME/day, with depression: aOR=7.06, (5.30-9.42) ≥100 MME/day, without depression aOR=4.34 (3.37-5.57)	Multivariable model included age, sex, region, pain conditions, mental health and substance abuse conditions, days' supply of benzodiazepines, zolpidem, and antidepressants
Zedler, 2014[25]	VHA medical and pharmacy claims data	Case-control	Veterans who were dispensed opioids	Maximum prescribed daily dose in 6 months prior to overdose (index date)	Serious opioid-related toxicity, including overdose, as identified in ICD-	20-49: aOR=1.5 (1 1-1.9)	Multivariable model included age, sex, race/ethnicity, marital status, Census region,

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			Cases: opioid overdose from October 1, 2010 to September 30, 2012 (N=817) Controls: 10 were matched to each case out of randomly selected group who had no overdose as of the case's overdose date (N=8,987)	1-19 (ref), 20-49, 50-99, >100	9-CM and CPT codes (N=817)	50-99: aOR=2.2 (1 5-3.2) ≥100: aOR=4.1 (2.6-6.5)	comorbidities, Rx opioid characteristics (formulation, route, active ingredient), selected nonopioid prescription medications, healthcare utilization
Dunn, 2010[19]	CONSORT Study, HMO-based study in Washington State: data linkage of (1) healthcare claims data and (2) state mortality records	Retrospective cohort	Adults (N=9,940) who filled ≥3 opioid prescriptions within first three months of opioid treatment for non-cancer pain, after ≥6 months with no opioid Rx, 1997-2005	1-19 (ref), 20-49, 50-99, ≥100	Opioid overdose, identified from ICD-9 codes in healthcare claims or ICD-10 codes in mortality records (N=51)	20-49:aHR=1.44 (0.57-3.62) 50-99: aHR=3.73 (1.47-9.50) ≥100: aHR=8.87 (3.99-19.72)	Multivariable model included age, sex, tobacco use, depression diagnosis, type of pain diagnosis, Charlson Comorbidity index, RxRisk comorbidity score, days' supply of prescriptions for sedative-hypnotics

ADE, alcohol- and drug-related events; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; AUC, area under the curve; CART, Classification and Regression Tree analysis; CI, confidence interval; CNCP, chronic non-cancer pain; Dx, diagnosis; EOL, end-of-life; ER, extended-release; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Clinical Modification; IR, immediate-release; LA, long-acting; LT, long-term; MA, Massachusetts; MED, morphine-equivalent dose; MME, morphine milligram-equivalents; NDI, National Death Index; OR, odds ratio; Rx, prescription; Se, sensitivity; Sp, specificity; SUD, substance use disorder; WA, Washington